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PATENT
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Elvis DeLa Cerz

Printed name of person mailing correspondence

Signature of person mailing correspondence

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Antoniades et al.	Art Unit:	1809
Serial No.:	07/582,332	Examiner:	F. T. Moezie
Filed:	Sept. 13, 1990	Customer No.:	21559
Patent No.:	5,124,316		
Issued:	June 23, 1992		
Title:	METHOD FOR PERIODONTAL REGENERATION		

Mail Stop Patent Ext.
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Applicants enclose the following documents:

1. Application for Extension of Patent Term Under 35 U.S.C. § 156;
2. Five Certified Copies of the Application for Extension of Patent Term Under 35 U.S.C. § 156, including the exhibits;
3. Exhibits 1-14;
4. Certificate Under 37 C.F.R. § 3.73(b)
5. A check in the amount of $1,120.00; and
6. A return post card.

If there are any other charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: Apr. 16, 2005

Paul T. Clark
Reg. No. 30,162

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045

PATENT
ATTORNEY DOCKET NO. 50224/007001

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APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

In accordance with 35 U.S.C. § 156 and 37 C.F.R 1.710(b)(3), Applicants, President and Fellows of Harvard College, a Massachusetts charitable corporation having a place of business at 17 Quincy Street, Cambridge, Massachusetts, 02138, and BioMimetic Therapeutics, Inc. (formerly BioMimetic Pharmaceuticals, Inc.), a Delaware corporation having a place of business at 389-A Nichol Mill Lane, Franklin, TN 37067, (hereinafter "Applicants"), represent that they are the assignees of the entire interest in and to U.S. Patent No. 5,124,316, granted to Harry N.

Antoniades and Samuel E. Lynch by virtue of assignments recorded at Reel 5027, Frame 0090 and Reel 5027, Frame 0089 on February 27, 1989 (EXHIBIT 4), and an assignment executed on November 4, 2005 and filed on November 29, 2005 (EXHIBIT 5).

Applicants, through undersigned counsel, hereby apply for a 2.7 year (987 day) extension of the term of U.S. Patent No. 5,124,316 under 35 U.S.C. § 156 on the basis of the following information submitted in accordance with the provisions of Title 37 C.F.R. § 1.740(a)(1)-(15), set forth in the sequence of those subparagraphs. Filed herewith is a Certificate under 37 C.F.R. § 3.73(b) and a Power of Attorney authorizing the undersigned to file and prosecute this Application for Extension of Patent Term, and to transact all business in relation thereto.

(1) Complete identification of the approved product by appropriate chemical and generic name, physical structure or characteristics

As a medical device[1], the approved product qualifies for patent term extension under 37 C.F.R 1.710(b)(3). In particular, the product is Biomimetic Therapeutics' synthetic grafting system for bone and periodontal regeneration. The system combines: (1) synthetic beta-tricalcium phosphate ($[Ca_3(PO_4)]$; hereinafter "β-TCP"), a highly porous bone void filler that serves as the osteoconductive matrix; and (2) highly purified, recombinant human platelet-derived growth factor composed of two disulfide-linked B-chain polypeptides (hereinafter "rhPDGF-BB"), which serves to enhance the physical properties of β-TCP by promoting bone and ligament cell proliferation (mitogenesis), cell migration (chemotaxis) into the wound and matrix, and revascularization (angiogenesis) of the surgical site.

1 As discussed below, the product was reviewed by the FDA as a combination product whose primary mode of action is its medical device component.

The system is marketed under the tradename "*GEM 21S*® Growth-factor Enhanced Matrix," and is provided as a kit containing (1) a container of 0.5 cc of β-TCP particles (0.250 to 1.0 mm); and (2) a solution of 0.5 ml rhPDGF-BB (0.3 mg/ml in a sodium acetate buffer) contained in a syringe. All of the components are supplied sterile. The product is prepared for use by fully saturating the β-TCP with the rhPDGF-BB solution. Following the preparation of a tissue flap to expose the osseous defect and thorough debridement and root planing of the osseous defect, the prepared product is packed into the osseous defect. The tissue flap is secured with interdental sutures to achieve complete coverage of the surgical site, and the damaged bone is allowed to regrow.

(2) A complete identification of the federal statute including the applicable provision of law under which the regulatory review occurred

GEM 21S® Growth-factor Enhanced Matrix was reviewed as a combination product and the federal statute under which the regulatory review occurred is § 503(g) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 353(g)). In accordance with the provisions of §503(g), the U.S. Food and Drug Administration determined that in view of the primary mode of action of *GEM 21S*®, the product was further reviewed as a class III medical device under § 515 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 360(e)).

(3) The date on which the product received permission for commercial marketing or use under the provision of law which the applicable regulatory review period occurred

The Pre-Marketing Application (PMA) under 21 U.S.C. §§ 353(g) and 360(e) for the *GEM 21S®* product was approved on November 18, 2005. (EXHIBIT 6)

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved

GEM 21S® Growth-factor Enhanced Matrix is not a drug product, but was classified by the Food and Drug Administration ("FDA") as a combination product in that it includes both a drug component (rh-PDGF-BB) and a medical device component (β-tricalcium phosphate particulate (β-TCP)). Because the FDA concluded that the primary mode of action of *GEM 21S®* is the medical device component (β-TCP), *GEM 21S®* was reviewed by the FDA as a class III medical device.

Two different formulations of rh-PDGF-BB were previously reviewed by the FDA – Becaplermin and Regranex® Gel. Becaplermin is a bulk rh-PDGF-BB product manufactured by Chiron Corporation and is provided as a bulk raw material. Becaplermin was reviewed by the FDA as a biological product (and not as a drug or combination product) under the Public Health Service Act (42 U.S.C. § 262). Becaplermin Concentrate was reviewed under BLA No. 96-1422; Biologics License No. 1106 and was approved on December 16, 1997. (EXHIBIT 7) Becaplermin Concentrate was only approved for manufacture under a shared manufacturing

arrangement with OMJ Pharmaceuticals, Inc., and was not approved for commercial marketing to clinicians for use in its bulk formulation.

Regranex Gel is manufactured by OMJ Pharmaceuticals, and is a non-sterile, low bioburden, preserved, sodium carboxymethylcellulose based (CMC) topical gel, containing 100μg of Becaplermin per gram of gel. Regranex Gel was approved for commercial marketing as a biological product (and not as a drug or combination product) under the Public Health Service Act (42 U.S.C. § 262). Regranex Gel was reviewed by the FDA under Biologics License Application (BLA) No. 96-1408; Biologics License No. 1196 was approved on December 16, 1997. (EXHIBIT 7) Regranex Gel was approved for treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have adequate blood supply. The package insert label for Regranex/Becaplermin is included herewith as EXHIBIT 8.

Applicants note that the regulatory review of Regranex/Becaplermin was the basis for extending the term of U.S. patent 4,845,075 (the "'075 patent") under 35 U.S.C. 156. A copy of the Application for Patent Extension for the '075 patent is attached hereto as EXHIBIT 9.

Applicants also note that other types of tricalcium phosphate medical devices have been approved by the FDA under 510(k) applications as Class II medical devices. However, the first β-TCP medical device to be approved for use in a dental application was reviewed as a Class III PMA product under the tradename Perio-Oss, and was approved for commercial use in 1981. (EXHIBIT 10) Since that time, β-TCP for dental use has been reclassified as a Class II Medical Device and all other products have been cleared for commercial use via the 510(k) route. It is important to note that neither Perio-Oss, nor any of the other Class II tricalcium phosphate medical devices were reviewed as combination products pursuant to 21 U.S.C. § 353(g).

The β-TCP particulate included in *GEM 21S*® is supplied by Orthovita Company. Orthovita markets a variety of β-TCP products under the tradename Vitoss™. Vitoss™ particulate is a Class II Medical Device and the subject of 510(k) numbers K994337 and K032409, which were cleared on December 14, 2000 and August 29, 2003, respectively. Vitoss™ particulate is cleared for use as a bone void filler for voids or gaps that are not intrinsic to the stability of the bony structure, and for use in the treatment of surgically created osseous defects or osseous defects created from traumatic injury to the bone. The Vitoss particulate 510(k)'s are classified under product code MQV as orthopedic products, and it is not a dental product such as *GEM 21S*®. Various documents relating to the approval of Vitoss™ particulate 510(k)'s are included in EXHIBIT 11.

Despite the previous approvals of Becaplermin, Regranex and various tricalcium phosphate products, *GEM 21S*® is the first product containing either rh-PDGF-BB or β-TCP to be reviewed by the FDA under § 503(g) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 353(g)) as a combination product. Furthermore, *GEM 21S*® is the first product containing rh-PDGF-BB to be approved by the FDA under 21 U.S.C. § 360(e) as a class III medical device.

(5) Statement that the present application is being submitted within the sixty day period permitted for submission and an identification of the date of the last day on which the application could be submitted

The present application for patent term extension is being submitted within the sixty day period permitted for submission pursuant to 37 C.F.R. § 1.720(f). The last day for submission of the present application is January 17, 2006.

(6) The complete identification of the patent for which an extension is being sought by the name of the inventors, the patent number, the date of issue, and the expiration date

The present application for extension is for U.S. Patent No. 5,124,316 (U.S. Serial No. 07/582,332) issued on June 23, 1992 and expiring on June 23, 2009. The inventors are Harry N. Antoniades and Samuel E. Lynch.

(7) A copy of the entire patent for which extension is being sought, including the entire specification, claims, and drawings

A copy of U.S. Patent No. 5,124,316 is attached as (EXHIBIT 1).

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent

Receipts of maintenance fee payments for U.S. Patent No. 5,124,316 for the after-grant periods of 3½, 7½, and 11½ years are attached as EXHIBIT 2. A copy of the Certificate of Correction issued in connection with U.S. Patent No. 5,124,316 is attached as EXHIBIT 3. No disclaimer or reexamination certificate has been issued in connection with U.S. Patent No. 5,124,316.

(9) Statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on a method of using the approved product

U.S. Patent No. 5,124,316 includes only one claim, which reads:

A method of promoting growth of damaged bone, periodontium, or ligament of a living mammal, comprising the steps of

producing a surgical flap of skin to expose said damaged bone, periodontium, or ligament,

planing said damaged bone or periodontium to remove organic matter from said bone or periodontium

applying platelet derived growth factor in a pharmaceutically acceptable carrier to said exposed bone, periodontium, or ligament,

replacing said flap, and

allowing said damaged bone, periodontium, or ligament to regrow.

The approved product, "*GEM 21S®*," is a system for treating periodontally-related bone defects. A copy of the approved package insert is attached hereto as EXHIBIT 12. As indicated in the package insert, *GEM 21S®* is composed of two sterile components:

(1) Synthetic beta-tricalcium phosphate (ß-TCP) [Ca3 (PO4)], which is a highly porous, resorbable osteoconductive scaffold or matrix that provides a framework for bone ingrowth, and

(2) Highly purified, recombinant human platelet-derived growth factor-BB (rhPDGF-BB).

In addition, as reflected in the package insert, *GEM 21S®* is indicated to treat the following periodontally-related defects:

- Intrabony periodontal defects;
- Furcation periodontal defects; and
- Gingival recession associated with periodontal defects.

The following table illustrates how the surgical technique as outlined in the *GEM 21S®* package insert practices the invention claimed in the '316 patent. This table is provided merely for illustrative purposes as a single embodiment covered by claim 1 of the '316 patent, and is not intended to in any way restrict the interpretation of claim 1 with regard to other embodiments:

'316 Claim	*GEM 21S*® Surgical Techniques
producing a surgical flap of skin to expose said damaged bone, periodontium, or ligament	Following exposure of the defect with a full thickness mucoperiosteal flap, all granulation tissue must be carefully removed.
planing said damaged bone or periodontium to remove organic matter from said bone or periodontium	Thorough soft tissue debridement of the defect is critical to successful regeneration. Granulation tissue, if left in the defect, could be stimulated by the rhPDGF-BB component, diminishing the desired regenerative response. Exposed tooth root surfaces should also be thoroughly planed.
applying platelet derived growth factor in a pharmaceutically acceptable carrier to said exposed bone, periodontium, or ligament	Following thorough debridement of the osseous defect, the clinician, based on his or her experience, estimates the amount of *GEM 21S*® needed to fill the defect. For best results, *GEM 21S*® must completely fill the defect to the level of the surrounding bony walls. Overfilling should be avoided. The clinician prepares the *GEM 21S*® graft by fully saturating the ß-TCP particles with the rhPDGF-BB solution and letting the product sit for approximately ten (10) minutes. Proper aseptic technique must be employed in preparing and applying *GEM 21S*®. The saturated *GEM 21S*® should be placed into the defect using moderate pressure, taking care not to crush the particles. In order to enhance the formation of new bone, *GEM 21S*® should be placed in direct contact with well-vascularized bone. Excessive bleeding should be controlled prior to placing grafting materials.
replacing said flap	Following placement of the *GEM 21S*® and completion of any additional surgical steps, the mucoperiosteal flaps should be sutured to achieve primary closure wherever possible.
allowing said damaged bone, periodontium, or ligament to regrow	Postoperative patient management should follow the same regimen as similar cases utilizing autogenous bone grafting. Pre-requisites for all regenerative procedures include prevention of wound dehiscence, a stable clot and minimal bacterial contamination.

Thus, claim 1 reads on the approved method of using *GEM 21S®*.

(10) The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period, as set forth in 37 C.F.R. § 1.740(a)(10)(v):

A) The effective date of the investigational device exemption (IDE) and the IDE number, if applicable

An IDE (No. 6010340) for *GEM 21S®* was conditionally approved on February 28, 2002. This conditional approval permitted initiation of patient enrollment in the *GEM 21S®* pivotal clinical study. The IDE was given final approval on April 24, 2002.

B) The date on which the application for product approval or notice of completion of a product development protocol under § 515 of the Federal Food, Drug and Cosmetic Act was initially submitted and the number of the application

1) A Pre-market Approval application (PMA) for *GEM 21S®* was submitted on March 12, 2004.

2) The PMA number is P040013.

C) The date on which the application was approved or the protocol declared to be completed

The *GEM 21S®* PMA was approved on November 18, 2005.

(11) Brief description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities

A brief description of the significant activities undertaken by the marketing applicant, Biomimetic Therapeutics, Inc, and the applicable dates are provided in chronological order as EXHIBIT 13. It should be noted that the IDE and PMA for *GEM 21S*® were filed in the name of BioMimetic Pharmaceuticals, Inc. In August 2005, Biomimetic Pharmaceuticals, Inc. changed its name to BioMimetic Therapeutics, Inc., the current applicant hereunder and co-owner of the '316 patent. A copy of the certificate of name change is attached hereto as EXHIBIT 14.

(12) Statement that in the opinion of the applicant the patent is eligible for extension and a statement as to the length of extension claimed, including how the extension was calculated

Applicants are of the opinion that U.S. Patent No. 5,124,316 is eligible for extension under 35 U.S.C. § 156 because it satisfies all the requirements for such an extension in as much as:

(i) the term of such patent has not expired before submission of this application (35 U.S.C. § 156(a)(1));

(ii) the term of such patent has never been extended (35 U.S.C. § 156(a)(2));

(iii) the application for extension is submitted by the owners of record, through undersigned counsel, in accordance with the requirements of 35 U.S.C. § 156(d) (35 U.S.C. § 156(a)(3));

(iv) the approved product, *GEM 21S*®, has been subject to a regulatory review period before its commercial marketing or use (35 U.S.C. § 156(a)(4));

(v) the permission for the commercial marketing or use of the product, *GEM 21S*®, after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of the Federal Food, Drug and Cosmetic Act under which such regulatory review period occurred (35 U.S.C. § 156(a)(5)); and

(vi) no other patent has been extended for the same regulatory review period for the approved product (35 U.S.C. § 156(c)(4)).

As noted above, components of *GEM 21S*® (Becaplermin and Vitoss) were previously approved for commercial marketing, but such approvals were for different "products" and were

under different statutory provisions than the statutory provisions under which the *GEM 21S®* regulatory review period occurred.

In particular, Becaplermin/Regranex was reviewed by the FDA under the provision of the Federal Food, Drug and Cosmetic Act relating to biological products (42 U.S.C. § 262). (See Application for Extension of Patent Term of US Patent 4,845,075, page 3, paragraph 2 (EXHIBIT 9).) Vitoss was reviewed under a 510(k) application as a class II medical device. (EXHIBIT 11) In contrast, the *GEM 21S®* product was reviewed by the FDA under 21 U.S.C. § 353(g) as a combination product, and in view of its primary mode of action was also reviewed under 21 U.S.C. §360(e) as a class III medical device.

Applicants submit that Becaplermin/Regranex and Vitoss are clearly different "products" as that term is used in 35 U.S.C. § 156(a)(5). Moreover, even if they were the same "product," *GEM 21S®* was reviewed under different statutory provisions. Therefore, the *GEM 21S®* product "is the first permitted commercial marketing or use of the *product under the provision of the Federal Food, Drug and Cosmetic Act under which such regulatory review period occurred*" as required under 35 U.S.C. § 156(a)(5) (emphasis added).

Applicants request an extension of the patent term of U.S. Patent No. 5,124,316 by 2.7 years (987 days) from the original expiration date of June 23, 2009 to March 6, 2012. This period of extension is calculated pursuant to 37 C.F.R. § 1.777 as follows:

Calculation of Patent Term Extension For
a Medical Device Under 37 C.F.R. § 1.777

Conditional Approval of IDE			February 28, 2002
PMA Filed March 12, 2004		(c)(1)	743 days
PMA Approved November 18, 2005		(c)(2)	616 days
Reg. Rev. Period	Total		1359 days
The subject patent issued June 23, 1992 before the IDE was filed		(d)(1)(i)	0 days
Applicants acted with due diligence at all relevant times		(d)(1)(ii)	0 days
One-half the number of days remaining in the Period defined by (c)(1) after being reduced by (d)(1)(i) · $\frac{743-0}{2}$ = (d)(1)(iii)			371 days
Regulatory Review Period: 1359 – 371 =			987 days
Original patent issued June 23, 1992 and is set to expire June 23, 2009 plus 987 days		(d)(2)	March 6, 2012
PMA Approval October 1, 2005 + 14 years		(d)(3)	October 1, 2019
Earlier of (d)(2) and (d)(3)		(d)(4)	March 6, 2012
Original issue date June 23, 2009 + 5 years		(d)(5)(i)	June 23, 2014
Earlier of date obtained pursuant to (d)(4) and (d)(5)(i)		(d)(5)(ii)	March 6, 2012
The original patent was issued after September 24, 1984		(d)(6)(i) (d)(6)(ii)	N/A N/A

Applicants respectfully submit that U.S. Patent No. 5,124,316 is eligible for a 987 day extension as calculated pursuant to 37 C.F.R. § 1.777. Therefore, Applicants respectfully request that the original expiration date of the patent be extended to March 6, 2012.

(13) Statement that the Applicants acknowledge a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension

Applicants, through undersigned counsel, acknowledge a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determinations to be made relative to the application for extension, in accordance with 37 C.F.R. § 1.765.

(14) The prescribed fee for receiving and acting upon the application for extension

A check in the amount of $1,120.00 for payment of the patent term extension application fee, pursuant to 37 C.F.R. § 1.20(j)(1) is enclosed. If there are any other charges or any credits, please apply them to Deposit Account No. 03-2095.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed

Please direct all inquiries and correspondence relating to this application for patent term extension to:

Paul T. Clark

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045

Respectfully submitted,

Date: Dec. 16, 2005

Paul T. Clark
Reg. No. 30,162

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045

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ATTORNEY DOCKET NO. 50224/007001

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Date of Deposit: 12/16/05 Label Number: EV 768762375 US

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Elvis De La Cruz
Printed name of person mailing correspondence

Signature of person mailing correspondence

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Patent No.:	5,124,316		
Issued:	June 23, 1992		
Title:	METHOD FOR PERIODONTAL REGENERATION		

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE UNDER 37 C.F.R. § 3.73(b)

Pursuant to 37 C.F.R. § 3.73(b), President and Fellows of Harvard College, a Massachusetts charitable corporation having a place of business at 17 Quincy Street, Cambridge, Massachusetts, 02138, and BioMimetic Therapeutics, Inc., a Delaware corporation having a place of business at 389-A Nichol Mill Lane, Franklin, TN, certify that they are the assignees of the entire right, title, and interest in the above-captioned patent identified above.

Pursuant to 37 C.F.R. § 3.73(b)(2), this Certificate is signed by an attorney of record authorized to act on behalf of the assignees.

Pursuant to 37 C.F.R. § 3.73(b)(1)(ii), the undersigned attorney of record certifies that President and Fellows of Harvard College, a charitable corporation, and BioMimetic Therapeutics, Inc., a corporation, are the assignees of the entire right, title, and interest in the patent by virtue of:

An assignment from the inventors of the application. The assignment was Recorded in the U.S. Patent and Trademark Office at Reel/Frame 5027/0089 and 5027/0090 on February 27, 1989; copies of the executed assignments and notices of recordation are attached hereto; and

An assignment from the Institute of Molecular Biology executed on November 4, 2005 and filed with the U.S. Patent and Trademark Office on November 29, 2005; a copy of the executed assignment is attached hereto.

The undersigned has reviewed all the documents in the chain of title of the patent identified above and, to the best of undersigned's knowledge and belief, title is in the assignees identified above. The undersigned (whose title is supplied below) is empowered to act on behalf of the assignees.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity

of the application or any patents issued thereon.

Respectfully submitted,

Date: Dec. 16, 2005

Paul T. Clark
Reg. No. 30,162

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045

ASSIGNMENT

For valuable consideration, I, Samuel (FIRST) E. (MIDDLE INITIAL) Lynch (LAST)

of Jamaica Plain (CITY OR TOWN), Massachusetts (STATE) hereby assign

to THE PRESIDENT AND FELLOWS OF HARVARD COLLEGE, a

Massachusetts corporation having a place of business

at Cambridge, Massachusetts,

and its successors and assigns (collectively hereinafter called "the Assignee"), the entire right, title and interest throughout the world in the inventions and improvements which are the subject of an application for United States Serial No. 299,763 filed January 20, 1989, entitled WOUND HEALING

this assignment including said application, any and all United States and foreign patents granted for any of said inventions or improvements, and the right to claim priority based on the filing date of said application under the International Convention for the Protection of Industrial Property, the Patent Cooperation Treaty, the European Patent Convention, and all other treaties of like purposes; and I authorize the Assignee to apply in all countries in my name or in its own name for patents and like rights of exclusion and for inventor's certificates for said inventions and improvements; and I agree for myself and my heirs, legal representatives and assigns, without further compensation to perform such lawful acts and to sign such further applications, assignments, Preliminary Statements and other lawful documents as the Assignee may reasonably request to effectuate fully this assignment.

In Witness Whereof, I hereto set my hand and seal at Boston, Massachusetts, this 17 day of February, 1989.

Samuel E. Lynch L.S.
(FIRST) (MIDDLE INITIAL) (LAST)

State of Massachusetts :
ss.
County of Suffolk :

Before me this 17 day of February, 19 89, personally appeared Samuel E. Lynch known to me to be the person whose name is subscribed to the foregoing Assignment and acknowledged that he executed the same as his free act and deed for the purposes therein contained.

Deborah A. Mackenzie
Notary Public

[Notary's seal here]

RECORDED
PATENT & TRADEMARK OFFICE
FEB 27 89

My commission expires: Nov. 16, 1995

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UNITED STATES PATENT OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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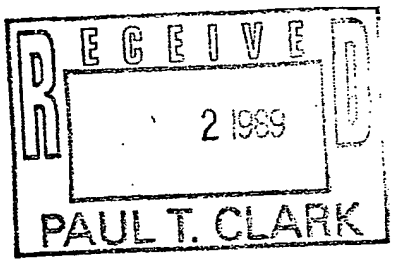

TO: PAUL T. CLARK
FISH & RICHARDSON
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UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME NUMBER REFERENCED BELOW. A DIGEST OF THE DOCUMENT HAS ALSO BEEN MADE AND APPEARS IN THE OFFICE'S RECORDS AS SHOWN:

ASSIGNOR: 001 ANTONIADES, HARRY N. DOC DATE: 02/17/89

RECORDATION DATE: 02/27/89 NUMBER OF PAGES 001 REEL/FRAME 5027/0090

DIGEST: ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE: 501 INSTITUTE OF MOLECULAR BIOLOGY, THE, BOSTON, MA., A DE. CORP.

SERIAL NUMBER 7-299763 FILING DATE 01/23/89
PATENT NUMBER ISSUE DATE 00/00/00

TITLE OF INVENTION: WOUND HEALING

INVENTOR: 001 ANTONIADES, HARRY N.
INVENTOR: 002 LYNCH, SAMUEL E.

ASSIGNMENT

For valuable consideration, I, Harry (FIRST) N. (MIDDLE INITIAL) Antoniades (LAST)

of Newton (CITY OR TOWN), Massachusetts (STATE) hereby assign

to THE INSTITUTE OF MOLECULAR BIOLOGY, Inc., a

Delaware corporation having a place of business

at Boston, Massachusetts,

and its successors and assigns (collectively hereinafter called "the Assignee"), the entire right, title and interest throughout the world in the inventions and improvements which are the subject of an application for United States ~~Patent signed by me~~ Serial No. 299,763 filed January 20, 1989 ~~this day~~, entitled WOUND HEALING

this assignment including said application, any and all United States and foreign patents granted for any of said inventions or improvements, and the right to claim priority based on the filing date of said application under the International Convention for the Protection of Industrial Property, the Patent Cooperation Treaty, the European Patent Convention, and all other treaties of like purposes; and I authorize the Assignee to apply in all countries in my name or in its own name for patents and like rights of exclusion and for inventor's certificates for said inventions and improvements; and I agree for myself and my heirs, legal representatives and assigns, without further compensation to perform such lawful acts and to sign such further applications, assignments, Preliminary Statements and other lawful documents as the Assignee may reasonably request to effectuate fully this assignment.

In Witness Whereof, I hereto set my hand and seal at Boston, Massachusetts, this 17 day of February, 1989.

Harry N. Antoniades L.S.

(FIRST) Harry (MIDDLE INITIAL) N. (LAST) Antoniades

State of Massachusetts :
ss.
County of Suffolk :

Before me this 17 day of February, 19 89, personally appeared Harry N. Antoniades known to me to be the person whose name is subscribed to the foregoing Assignment and acknowledged that he executed the same as his free act and deed for the purposes therein contained.

Deborah C. Michaels
Notary Public

[Notary's seal here]

My commission expires: Nov 16, 1995

RECORDED
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REEL 5027 FRAME 090

UNITED STATES DEPARTMENT OF COMMERCE
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TO: PAUL T. CLARK
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UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

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ASSIGNOR: 001 LYNCH, SAMUEL E. DOC DATE: 02/17/89

RECORDATION DATE: 02/27/89 NUMBER OF PAGES 001 REEL/FRAME 5027/0089

DIGEST: ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE: 501 PRESIDENT AND FELLOWS OF HARVARD COLLEGE, THE, CAMBRIDGE, MA., A MA. CORP.

SERIAL NUMBER 7-299763 FILING DATE 01/23/89
PATENT NUMBER ISSUE DATE 00/00/00

TITLE OF INVENTION: WOUND HEALING

INVENTOR: 001 ANTONIADES, HARRY N.
INVENTOR: 002 LYNCH, SAMUEL E.

ASSIGNMENT

For valuable consideration, we,

Full Name of Assignor	City	State (and Country if not USA)
Institute of Molecular Biology, Inc.	Delaware	P.O. Box 4278 Shrewsbury, MA 01545

hereby assign to

Full Name of Assignee	State of Incorporation	Business Address
BioMimetic Therapeutics, Inc.	Delaware	389 Nichol Mill Lane Franklin, TN 37067

and to its successors and assigns (collectively hereinafter called "the Assignee"), the entire right, title, and interest throughout the world in the inventions and improvements which are the subject of one or more of the patents and applications listed on Schedule A, which is attached hereto.

This assignment includes the patents and applications listed in the attached Schedule A, any and all United States and foreign patents, utility models, and design registrations granted for any of said inventions or improvements, and the right to claim priority based on the filing date of any of the patents and applications listed in the attached Schedule A under the International Convention for the Protection of Industrial Property, the Patent Cooperation Treaty, the European Patent Convention, and all other treaties of like purposes; and we authorize the Assignee to apply in all countries in our names or in its own name for patents, utility models, design registrations, and like rights of exclusion, and for inventors' certificates for said inventions and improvements; and we agree for ourselves and our respective heirs, legal representatives and assigns, without further compensation, to perform such lawful acts and to sign such further applications, assignments, Preliminary Statements, and other lawful documents as the Assignee may reasonably request to effectuate fully this assignment.

IN WITNESS WHEREOF, I hereto set my hand and seal at SHREWSBURY, MASSACHUSETTS, this 4th day of November, 2005

John M. Naples L.S.

John M. Naples, President
Institute of Molecular Biology, Inc.

STATE OF MASSACHUSETTS :

:ss.

COUNTY OF WORCESTER :

Before me this 4th day of November, 2005, before me, the undersigned notary public, personally appeared John M. Naples, proved to me through satisfactory evidence of identification, which consisted of MASSACHUSETTS DRIVERS LICENSE, to be the person whose name is subscribed to the foregoing Assignment, and acknowledged that he executed the same as his free act and deed for the purposes therein contained.

Notary Public

My Commission Expires: 020708

[Notary's Seal Here]

PATRICIA MacISAAC
Notary Public
Commonwealth of Massachusetts
My Commission Expires
February 7, 2008

Schedule A
(Page 1 of 5)

C&E Ref. No.	Status	Title	Application No.	Filed	Patent No.	Issued
02854-007001	Abandoned	WOUND HEALING AND BONE REGENERATION	06/930,762	14-Nov-1986		
02854-009001	Issued	WOUND HEALING AND BONE REGENERATION USING PDGF AND IGF-1	07/120,943	16-Nov-1987	4,861,757	29-Aug-1989
02854-010001	Issued	WOUND HEALING COMPOSITION OF TGF-ALPHA AND PDGF	07/136,399	22-Dec-1987	4,874,746	17-Oct-1989
02854-011001	Issued	WOUND HEALING USING IGF-I AND TGFβ	07/196,975	20-May-1988	4,983,581	8-Jan-1991
02854-011002	Abandoned	WOUND HEALING USING IGF-I AND TGFβ	07/530,649	30-May-1990		
02854-011003	Issued	WOUND HEALING USING IGF-II AND TGF	07/857,713	25-Mar-1992	5,256,644	26-Oct-1993
02854-012001	Issued	PROCESS OF WOUND HEALING USING PDGF AND EGF	07/231,145	10-Aug-1988	5,034,375	23-Jul-1991
02854-013003	Abandoned	WOUND HEALING	07/449,303	5-Dec-1989		
02854-013004	Abandoned	WOUND HEALING	07/639,060,303	9-Jan-1991		
02854-014001	Issued	WOUND HEALING USING PDGF AND IGF-II	07/272,090	16-Nov-1988	5,019,559	28-May-1991
02854-015001	Abandoned	WOUND HEALING	07/299,763	23-Jan-1989		
02854-015002	Issued	METHOD OF PERIDONTAL REGENERATION	07/582,332	13-Sep-1990	5,124,316	23-Jun-1992
02854-016001	Issued	WOUND HEALING COMPOSITION OF IL-1 AND PDGF OR IGF-1	07/403,969	7-Sep-1989	5,035,887	30-Jul-1991
02854-026001	Abandoned	BONE REGENERATION	07/799,375	27-Nov-1991		
02854-027001	Issued	NERVE REGENERATION	08/198,542	18-Feb-1994	6,506,727	14-Jan-2003
02854-033001	Issued	DEVICE TO PROMOTE DRUG-INDUCED NERVE REGENERATION	08/187,210	26-Jan-1994	5,656,605	12-Aug-1997
02854-034001	Issued	PYRIDINOLINE CROSSLINKS AS MARKERS OF PERIODONTAL AND PERI-IMPLANT DISEASE ACTIVITY	08/197,131	16-Feb-1994	5,516,699	14-May-1996

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KC&R Ref. No.	Country	Type	Status	Application No.	Filed	R. Patent No.	Issued
WOUND HEALING AND BONE REGENERATION							
02854-007AT1	Austria	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007AU1	Australia	PCT	Granted	83289/87	13-Nov-1987	600069	02-Aug-1990
02854-007BE1	Belgium	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007CA1	Canada	PCT	Granted	551,909	16-Nov-1987	1,322,714	05-Oct-1993
02854-007CH1	Switzerland	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007CN1	China	PCT	Granted	87101250.2	14-Nov-1987	87101250.2	30-Oct-1994
02854-007DE1	Germany	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007DK1	Denmark	PCT	Granted	3932/88	13-Nov-1987	25-Jul-81	30-May-05
02854-007EP1	Europe	PCT	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007FR1	France	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007FR2	France	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-007GB1	Great Britain	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007IE1	Ireland	PCT	Granted	3075/87	13-Nov-1987	60517	20-Jul-1994
02854-007IT1	Italy	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007JP1	Japan	PCT	Granted	500179/87	13-Nov-1987	1868245	26-Aug-1994
02854-007KR1	Korea	PCT	Granted	88-700829	13-Nov-1987	106280	17-Oct-1996
02854-007LU1	Luxembourg	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007NL1	Netherlands	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007NZ1	New Zealand	PCT	Granted	222551	16-Nov-1987	222551	
02854-007SE1	Sweden	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007TW1	Taiwan	PCT	Granted	76107672	15-Dec-1987	NI-51493	30-Jan-1992
02854-007ZA1	South Africa	PCT	Granted	87/8566	16-Nov-1987	87/8566	26-Jul-1989
02854-007OA1	Africa (OAPI)	PCT	Abandoned	PV59385	13-Nov-1987	9159	31-Mar-1992
02854-007MX1	Mexico	PCT	Abandoned	930672	16-Nov-1987	170454	23-Aug-1993
02854-007NO1	Norway	PCT	Abandoned	88/3127	13-Nov-1987		
02854-007WO1	International	PCT	Expired	PCT/US87/02975	13-Nov-1987		
WOUND HEALING							
02854-010AT1	Austria	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010AU1	Australia	PCT	Granted	37472/89	20-Dec-1988	613776	03-Dec-1991
02854-010BE1	Belgium	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010CA1	Canada	PCT	Granted	586,562	21-Dec-1988	1,322,164	14-Sep-1993
02854-010CH1	Switzerland	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010CN1	China	PCT	Granted	88109273.8	21-Dec-1988	88109273.8	19-Jul-1994
02854-010DE1	Germany	EPC	Granted	89901681.0	20-Dec-1988	P3885300.0	27-Oct-1993
02854-010DK1	Denmark	PCT	Granted	4122/89	20-Dec-1988	175947	08-Aug-2005
02854-010EP1	Europe	PCT	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010FR1	France	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010GB1	Great Britain	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010IE1	Ireland	PCT	Granted	3833/88	21-Dec-1988	61283	14-Oct-1994
02854-010IT1	Italy	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010JP1	Japan	PCT	Granted	501944/89	20-Dec-1988	1923551	25-Apr-1995
02854-010LU1	Luxembourg	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010MX1	Mexico	PCT	Granted	14307	22-Dec-1988	164966	09-Oct-1992
02854-010NL1	Netherlands	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010NZ1	New Zealand	PCT	Granted	227429	21-Dec-1988	227429	14-May-1991
02854-010SE1	Sweden	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010TW1	Taiwan	PCT	Granted	78100693	01-Feb-1989	NI-51930	20-Feb-1992
02854-010ZA1	South Africa	PCT	Granted	88/9594	22-Dec-1988	88/9594	27-Sep-1989
02854-010OA1	Africa (OAPI)	PCT	Abandoned	PV59630	20-Dec-1988	9129	31-Oct-1991
02854-010KR1	Korea	PCT	Abandoned	89/701555	20-Dec-1988		
02854-010NO1	Norway	PCT	Abandoned	89/3346	20-Dec-1988		
02854-010RU1	Russian Federation	PCT	Abandoned	4742130.14	20-Dec-1988		
02854-010WO1	International	PCT	Expired	PCT/US88/04557	20-Dec-1988		

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C & E Ref. No.	Country	Type	Status	Application No.	Date Filed	Patent No.	Date Issued
WOUND HEALING							
02854-011AT1	Austria	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011AT2	Austria	EPC	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011BE1	Belgium	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011BE2	Belgium	EPC	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011CA2	Canada	PCT	Granted	2,082,420	30-May-1991	2082420	20-Jul-2004
02854-011CH1	Switzerland	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011CH2	Switzerland	EPC	Granted	91910904.1	30-May-1991	531425	14-Aug-2002
02854-011DE1	Germany	EPC	Granted	89906917.3	22-May-1989	P68917300.8	03-Aug-1994
02854-011DE2	Germany	EPC	Granted	69133087.5	30-May-1991	0531425	14-Aug-2002
02854-011DK2	Denmark	EPC	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011EP1	Europe	PCT	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011EP2	Europe	PCT	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011ES2	Spain	EPC	Granted	0531425	30-May-1991	0531425	14-Aug-2002
02854-011FR1	France	EPC	Granted	0419534	22-May-1989	0419534	03-Aug-1994
02854-011FR2	France	EPC	Granted	0531425	30-May-1991	0531425	14-Aug-2002
02854-011GB1	Great Britain	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011GB2	Great Britain	EPC	Granted	0531425	30-May-1991	0531425	14-Aug-2002
02854-011GR2	Greece	EPC	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011IT1	Italy	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011IT2	Italy	EPC	Granted	0531425	30-May-1991	0531425	14-Aug-2002
02854-011JP1	Japan	PCT	Granted	506485/89	22-May-1989	1924479	25-Apr-1995
02854-011JP2	Japan	PCT	Granted	3-510861	30-May-1991	3,377,524	06-Dec-2002
02854-011LI2	Liechtenstein	EPC	Granted	91910904.1	30-May-1991	531425	14-Aug-2002
02854-011LU1	Luxembourg	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011LU2	Luxembourg	EPC	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011NL1	Netherlands	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011NL2	Netherlands	EPC	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011SE1	Sweden	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011SE2	Sweden	EPC	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011ES1	Spain	PCT	Abandoned	531425	30-May-1991		
02854-011WO1	International	PCT	Expired	PCT/US89/02229	22-May-1989		
02854-011WO2	International	PCT	Expired	PCT/US91/03829	30-May-1991		
WOUND HEALING							
02854-012AT1	Austria	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012BE1	Belgium	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012CA1	Canada	PCT	Granted	607,968	10-Aug-1989	1336816	29-Aug-1995
02854-012CH1	Switzerland	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012DE1	Denmark	EPC	Granted	89910545.6	10-Aug-1989	P68912758	26-Jan-1994
02854-012DE1	Germany	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012EP1	Europe	PCT	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012FR1	France	EPC	Granted	89910545.6	10-Aug-1989	382841	26-Jan-1994
02854-012GB1	Great Britain	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012IT1	Italy	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012JP1	Japan	PCT	Granted	509811/89	10-Aug-1989	1975393	27-Sep-1995
02854-012LU1	Luxembourg	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012NL1	Netherlands	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012SE1	Sweden	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012WO1	International	PCT	Expired	PCT/US89/03490	10-Aug-1989		

Schedule A
(Page 4 of 5)

C & E Ref No.	Country	Type	Status	Application No.	Filed	Ratent No.	Issued
WOUND HEALING USING PDGF AND IGF-II							
02854-014AT1	Austria	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014BE1	Belgium	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014CA1	Canada	PCT	Granted	2,060,208	10-Apr-1990	2,060,208	20-Feb-2001
02854-014CH1	Switzerland	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014DE1	Germany	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014DK1	Denmark	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014EP1	Europe	PCT	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014ES1	Spain	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014FR1	France	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014GB1	Great Britain	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014IT1	Italy	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014JP1	Japan	PCT	Granted	507475/90	10-Apr-1990	2030420	19-Mar-1996
02854-014LU1	Luxembourg	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014NL1	Netherlands	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014SE1	Sweden	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014WO1	International	PCT	Expired	PCT/US90/01936	10-Apr-1990		
WOUND HEALING							
02854-016CA1	**Canada**	**PCT**	**Pending**	**2,040,410**	**07-Sep-1990**		
02854-016JP1	Japan	PCT	Granted	2-512565	07-Sep-1990	1969836	18-Sep-1995
02854-016EP1	Europe	PCT	Abandoned	90913582.4	07-Sep-1990		
02854-016WO1	International	PCT	Expired	PCT/US90/05062	07-Sep-1990		
BONE REGENERATION							
02854-026CA1	Canada	PCT	Abandoned	2,123,803	24-Nov-1992		
02854-026JP1	Japan	PCT	Abandoned	Hei-05-510253	26-May-1994		
02854-026EP1	Europe	PCT	Abandoned	93900683.9	24-Nov-1992		
02854-026WO1	International	PCT	Expired	PCT/US92/10214	24-Nov-1992		
MEDICAMENT FOR PROMOTING GROWTH OF MAMMALIAN NERVE - IMB Only							
02854-027AU1	Australia	PCT	Granted	30668/92	04-Nov-1992	673659	12-Mar-1997
02854-027CA1	Canada	PCT	Granted	2,123,685	04-Nov-1992	2,123,685	07-Oct-2003
02854-027CH1	Switzerland	PCT	Granted	2309/93-2	04-Nov-1992	684573	31-Oct-1994
02854-027JP1	Japan	PCT	Allowed	5-510115	04-Nov-1992		
02854-027JP2	Japan	PCT	Pending	2005-292267	28-Sep-2005		
02854-027EP1	Europe	PCT	Abandoned	92924312.9	04-Nov-1992		
02854-027PL1	Poland	PCT	Abandoned	P303981	04-Nov-1992		
02854-027ZA1	South Africa	PCT	Abandoned		04-Nov-1992		
02854-027WO1	International	PCT	Expired	PCT/US92/09545	04-Nov-1992		

Schedule A
(Page 5 of 5)

C & E Ref No.	Country	Type	Status	Application Nos.	Filed	Patent Nos.	Issued
A DEVICE TO PROMOTE DRUG-INDUCED NERVE REGENERATION							
02854-033WO1	International	PCT	Expired	PCT/US95/00985	25-Jan-1995		
PYRIDINOLINE CROSSLINKS AS MARKERS OF PERIODONTAL AND PERI-IMPLANT DISEASE ACTIVITY							
02854-034AT1	Austria	EPC	Granted	95909234.7	13-Jan-1995	E220458	10-Jul-2002
02854-034BE1	Belgium	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034CA1	**Canada**	**PCT**	**Pending**	**2,183,452**	**13-Jan-1995**		
02854-034CH1	Switzerland	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034DE1	Germany	EPC	Granted	95909234.7	13-Jan-1995	69527350.7	10-Jul-2002
02854-034DK1	Denmark	PCT	Granted	95909234.7	13-Jan-1995	0745221	07-Oct-2002
02854-034EP1	Europe	PCT	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034ES1	Spain	EPC	Granted	95909234.7	13-Jan-1995	ES2179867T3	10-Jul-2002
02854-034FR1	France	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034GB1	Great Britain	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034GR1	Greece	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034IE1	Ireland	PCT	Granted	95909234.7	13-Jan-1995	0745221	
02854-034IT1	Italy	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034JP1	Japan	PCT	Granted	7-521795	13-Jan-1995	3,521,913	20-Feb-2004
02854-034KP1	N. Korea	PCT	Granted	96-0594	16-Aug-1996	31,331	22-Jan-1998
02854-034NL1	Netherlands	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034PT1	Portugal	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034PT1	Sweden	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034CN1	China	PCT	Abandoned	95192443.5	13-Jan-1995		
02854-034KR1	S. Korea	PCT	Abandoned	1996-704491	16-Aug-1996		
02854-034WO1	International	PCT	Expired	PCT/US95/00509	13-Jan-1995		

EXHIBITS

EXHIBIT 1	**COPY OF U.S. PATENT NO. 5,124,316**
EXHIBIT 2	**RECEIPTS OF MAINTENANCE FEE PAYMENTS FOR U.S. PATENT NO. 5,124,316**
EXHIBIT 3	**CERTIFICATE OF CORRECTION FOR U.S. PATENT NO. 5,124,316**
EXHIBIT 4	**ASSIGNMENTS FROM INVENTORS TO HARVARD AND INSTITUTE OF MOLECULAR BIOLOGY**
EXHIBIT 5	**ASSIGNMENT FROM INSTITUTE OF MOLECULAR BIOLOGY TO BIOMIMETIC THERAPEUTICS, INC.**
EXHIBIT 6	***GEM 21S®* APPROVAL LETTER**
EXHIBIT 7	**REGRANEX GEL/BECAPLERMIN APPROVAL LETTER**
EXHIBIT 8	**PACKAGE INSERT FOR REGRANEX/BECAPLERMIN**
EXHIBIT 9	**APPLICATION FOR PATENT EXTENSION FOR US PATENT NUMBER 4,845,075**
EXHIBIT 10	**PERIO-OSS PMA DATABASE ENTRY**
EXHIBIT 11	**VARIOUS DOCUMENTS RELATING TO THE APPROVAL OF VITOSS™ PARTICULATE 510(K)'S**
EXHIBIT 12	**GEM 21S® PACKAGE INSERT**
EXHIBIT 13	**FDA *GEM 21S®* CORRESPONDENCE CHRONOLOGY**
EXHIBIT 14	**CERTIFICATE OF NAME CHANGE FROM BIOMIMETIC PHARMACEUTICALS TO BIOMIMETIC THERAPEUTICS**

US005124316A

United States Patent [19]

Antoniades et al.

[11] Patent Number: 5,124,316

[45] Date of Patent: Jun. 23, 1992

[54] METHOD FOR PERIODONTAL REGENERATION

[75] Inventors: Harry N. Antoniades, Newton; Samuel E. Lynch, Jamaica Plain, both of Mass.

[73] Assignees: President and Fellows of Harvard College, Cambridge; Institute of Molecular Biology, Inc., Boston, both of Mass.

[21] Appl. No.: 582,332

[22] Filed: Sep. 13, 1990

Related U.S. Application Data

[63] Continuation of Ser. No. 299,763, Jan. 23, 1989, abandoned, which is a continuation-in-part of Ser. No. 234,196, Aug. 18, 1988, abandoned, which is a continuation-in-part of Ser. No. 120,606, Nov. 16, 1987, abandoned, which is a continuation-in-part of Ser. No. 930,762, Nov. 14, 1986, abandoned.

[51] Int. Cl.[5] A61K 37/02; A61K 7/16

[52] U.S. Cl. 514/12; 514/21; 514/2; 424/49; 604/54; 604/46; 604/77

[58] Field of Search 514/2, 3, 21, 12; 424/101, 49; 604/54, 46, 77

[56] References Cited

U.S. PATENT DOCUMENTS

4,702,734 10/1987 Terranova 604/54

FOREIGN PATENT DOCUMENTS

0312208 4/1989 European Pat. Off. .

Primary Examiner—F. T. Moezie
Attorney, Agent, or Firm—Fish & Richardson

[57] ABSTRACT

A method for promoting bone, periodontium or ligament growth of a mammal comprising applying to the bone periodontium or ligament a growth-promoting amount of a composition comprising a partially purified or purified polypeptide growth factor.

1 Claim, 1 Drawing Sheet

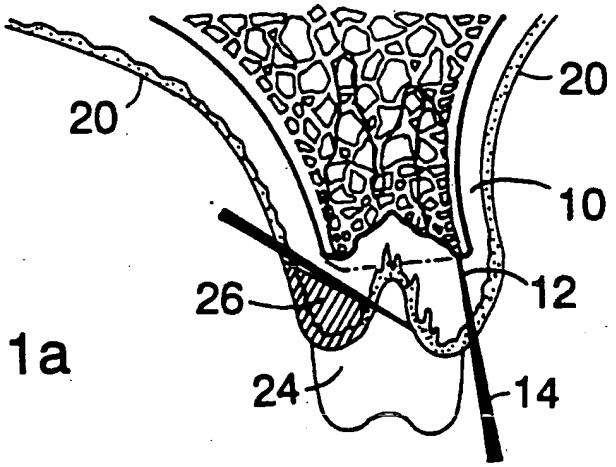

FIG. 1a

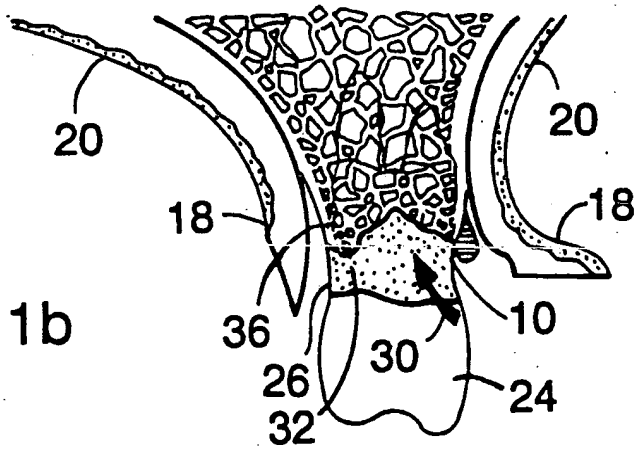

FIG. 1b

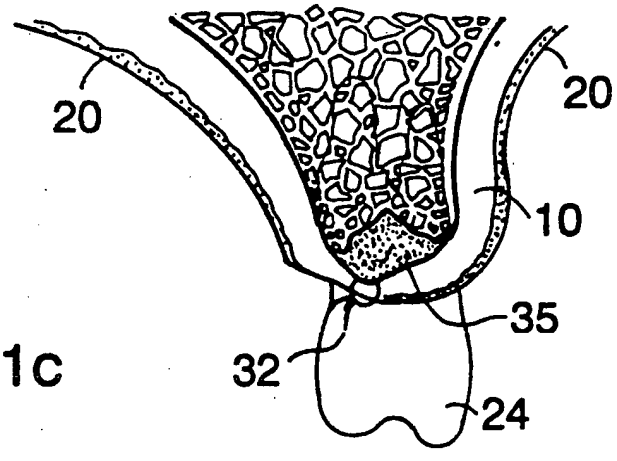

FIG. 1c

METHOD FOR PERIODONTAL REGENERATION

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Ser. No. 299,763, filed Jan. 23, 1989, which is a continuation-in-part of Antoniades et al., entitled "Wound Healing", U.S. Ser. No. 234,196, filed Aug. 18, 1988, which is a continuation-in-part of Antoniades et al., entitled "Wound Healing", U.S. Ser. No. 120,606, filed Nov. 16, 1987, which is a continuation-in-part of Antoniades et al., entitled "Healing External Wounds," U.S. Ser. No. 930,762, filed Nov. 14, 1986, all of which have been abandoned.

BACKGROUND OF THE INVENTION

This invention relates to the healing of bone and connective tissues.

Growth factors are polypeptide hormones which stimulate a defined population of target cells. Examples of growth factors include platelet-derived growth factor (PDGF), insulin-like growth factors (IGF-I and II), transforming growth factor beta (TGF-β), epidermal growth factor (EGF), and fibroblast growth factor (FGF). PDGF is a cationic, heat-soluble protein found in the granules of circulating platelets which is known to stimulate in vitro protein synthesis and collagen production by fibroblasts. It is also known to act as an in vitro mitogen and chemotactic agent for fibroblasts, smooth muscle cells, and glial cells.

It has been proposed to use PDGF to promote in vivo soft tissue wound healing. For example, Grotendorst (1984) J. Trauma 24:549–52 describes adding PDGF to Hunt-Schilling wire mesh chambers impregnated with a collagen gel and implanted in the backs of rats; PDGF was found to increase the amount of new collagen synthesized. However, Leitzel et al., (1985) J. Dermatol. Surg. Oncol. 11:617–22 were unable to accelerate normal wound healing in hamsters using PDGF alone or in combination with FGF and EGF.

Michaeli, et al. (1984) In *Soft and Hard Tissue Repair* (Hunt, T.K. et al., Eds), Praeger Publishers, New York, pp. 380–394, report that application of a partially purified preparation of PDGF obtained from platelet-rich plasma stimulated angiogenesis when implanted in rabbit corneas. Because PDGF is not an angiogenic growth factor the investigators suggested that an unknown factor in their partially purified PDGF preparation was responsible for the angiogenic effect.

Canalis (1985) Clin. Orthoped. Rel. Res. 193: 246–263 reports that PDGF stimulates DNA synthesis and nonspecific protein synthesis in calvariae in organ culture. In contrast, Tashijian, et al. (1982), Endocrinology 111:118 report that PDGF is a potent inducer of bone resorption in mouse calveria cultures. PDGF-stimulated bone resorption was mediated through increased prostaglandin production.

SUMMARY OF THE INVENTION

In a first aspect, the invention features a method for promoting bone, periodontium or ligament growth of a mammal. The method includes applying to the bone, periodontium or ligament a growth-promoting amount of a composition containing a partially purified or purified polypeptide growth factor.

In a related aspect, the invention features promoting periodontium or ligament growth of a mammal by applying to the periodontium or ligament a growth-promoting amount of a composition containing a partially purified or purified polypeptide growth factor or a partially purified or purified differentiation factor.

By polypeptide growth factor is meant a polypeptide, including a chain of at least 6 amino acids, which modulates the growth of one or more defined populations of target cells. By differentiation factor is meant a polypeptide, including a chain of at least 6 amino acids, which stimulates differentiation of one or more defined populations of target cells into cells with cartlidge or bone forming potential.

By promoting growth is meant to include healing of a wounded bone, periodontium or ligament, and regeneration of such tissues and structures. By promoting periodontium growth is meant to include regeneration or healing of the supporting tissues of a tooth including alveolar bone, cementum and interposed periodontal ligament, which have been damaged by disease or trauma.

In preferred embodiments, the step of applying includes applying a combination of a polypeptide growth factor and a differentiation factor; the polypeptide growth factor is chosen from platelet-derived growth factor, insulin-like growth factor I or insulin-like growth factor II, transforming growth factor β1, transforming growth factor β2, and transforming growth factor α; the differentiation factor is chosen from a bone morphogenetic protein (BMP) and osteogenin; most preferably the polypeptide growth factor is purified PDGF and the differentiation factor is partially purified or purified bone morphogenetic protein; the periodontium includes bone, cementum, and periodontal ligament; and the periodontium, bone, or ligament is damaged by disease or trauma, and the method includes applying to the mammal a disease-healing amount of the growth or differentiation factor.

In a related aspect, the invention features a method for preparing a composition for promoting growth of bone, periodontium or ligament. The method includes the step of mixing partially purified or purified platelet-derived growth factor in a pharmaceutically acceptable carrier substance.

In preferred embodiments, the pharmaceutically acceptable carrier substance is a natural or synthetic polymer, a bone substituting agent, or a viscous liquid or gel; most preferably the platelet derived growth factor is purified.

The compositions of this invention aid in regeneration of periodontium, at least in part, by promoting the growth of connective tissue, bone, and cementum, and by stimulating protein and collagen synthesis. Regeneration using a composition of this invention is a more effective treatment of periodontal diseases or bone wounds than that achieved using systemic antibiotics or surgical debridement alone.

In most preferred embodiments of the invention, the composition is prepared by combining partially purified or purified PDGF with a pharmaceutically acceptable carrier substance, e.g., natural and synthetic polymers (e.g., collagen, polyglycolic acid and polylactic acid), or bone substituting agents (e.g., tricalcium phosphate, hydroxyapatite, polymethylmethacrylate or demineralized freeze-dried cortical bone) or commercially available inert gels or liquids (e.g., methyl cellulose). In another most preferred embodiment, the invention features providing a composition including a combination

of purified PDGF and purified BMP in a pharmaceutically acceptable carrier substance.

The factors may be obtained from human tissues or cells, e.g., platelets, or by solid phase peptide synthesis, or by recombinant DNA technology. Thus, by the term "polypeptide growth factor" or "differentiation factor", we mean tissue or cell-derived, recombinant, and synthesized materials. If the factor is a dimer, e.g., PDGF, the recombinant factor can be a recombinant heterodimer, made by inserting into cultured prokaryotic or eukaryotic cells DNA sequences encoding both subunits of the factor, and then allowing the translated subunits to be processed by the cells to form a heterodimer. Alternatively, DNA encoding just one of the subunits (e.g., for PDGF preferably the beta or "2" chain) can be inserted into cells, which then are cultured to produce homodimeric factor (e.g., PDGF-1 or PDGF-2 homodimer).

The term "purified" as used herein refers to a growth or differentiation factor, e.g., PDGF, which, prior to mixing with a carrier substance, is 95% or greater by weight, i.e., the factor is substantially free of other proteins, lipids, and carbohydrates with which it is naturally associated. The term "partially purified" refers to a lesser purity of factor, having, for example, only 5%–95% by weight of the factor, preferably 65–95%.

A purified protein preparation will generally yield a single major band on a polyacrylamide gel. Most preferably, the purified factor used in compositions of the invention is pure as judged amino-terminal amino acid sequence analysis.

The composition of the invention provides a fast, effective method for healing bony wounds of mammals, e.g., fractures, implant recipient sites, and sites of periodontal disease. The composition enhances connective tissue and bone formation compared to natural healing (i.e., no exogenous agents added) or healing supplemented by addition of systemic antibiotics. Unlike natural healing, conventional surgical therapy, or antibiotics, the composition of the above factors in a carrier prompts increased bone, connective tissue, and cementum formation when applied to periodontal disease affected sites. The restoration of these tissues leads to an improved prognosis for the affected teeth. The ability of these factors to stimulate new bone formation also makes it applicable for treating bony defects caused by other types of infection or surgical or accidental trauma.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The drawings will first briefly be described.

DRAWINGS

FIG. 1 is a diagrammatic representation of a surgical procedure for periodontium regeneration.

Specifically, FIG. 1A shows an area of bone around a maxillary tooth which has been depleted by periodontal disease. Bone height in the absence of disease is shown by the dashed line. The arrows show surgical incision and reflection of gingival tissue.

FIG. 1B shows reflection of gingival tissue to expose a tooth root surface (covered by a mineralized layer of cementum) and bone. The root surface is cleaned by root planing. The arrow indicates the approximate area where a growth and/or differentiation factor is added in a pharmaceutically acceptable carrier substance to enhance regeneration or growth of bone, cementum and the interposed periodontal ligament.

FIG. 1C, shows suturing of gingival tissue. The shaded area indicates the position of placement of a growth and/or differentiation factor.

We now describe a preferred embodiment of the invention. Below is presented an example of use of PDGF as a bone and periodontum healing agent. As described above this example is not limiting to the invention, and those skilled in the art will recognize that the invention is broadly applicable as described in the Summary of the Invention and the claims.

EXAMPLE: PDGF

Osseous wounds, e.g., following periodontal disease or trauma, are treated, and peroidontium including bone, cementum, and connective tissue regenerated, according to the invention, with PDGF prepared by combining purified PDGF with any of the pharmaceutically acceptable carrier substances described above. Purified recombinant PDGF and purified PDGF derived from human platelets are commercially available from PDGF, Inc. (Boston, Mass.), Collaborative Research (Waltham, Mass.), and Amgen Corp. (Thousand Oaks, Calif.). Partially purified and purified PDGF can also be prepared as follows:

Five hundred to 1000 units of washed human platelet pellets are suspended in 1M NaCl (2 ml per platelet unit) and heated at 100° C. for 15 minutes. The supernatant is then separated by centrifugation and the precipitate extracted twice with the 1M NaCl.

The extracts are combined and dialyzed against 0.08M NaCl–0.01M sodium phosphate buffer (pH 7.4) and mixed overnight at 4° C. with CM-Sephadex C-50 equilibrated with the buffer. The mixture is then poured into a column (5×100 cm), washed extensively with 0.08M NaCl-0.01M sodium phosphate buffer (pH 7.4), and eluted with 1M NaCl while 10 ml fractions are collected.

Active fractions are pooled and dialyzed against 0.3M NaCl-0.01M sodium phosphate buffer (pH 7.4), centrifuged, and passed at 4° C. through a 2.5×25 cm column of Blue Sepharose (Pharmacia) equilibrated with 0.3M NaCl-0.01M sodium phosphate buffer (pH 7.4). The column is then washed with the buffer and partially purified PDGF eluted with a 1:1 solution of 1M NaCl and ethylene glycol.

The partially purified PDGF fractions are diluted (1:1) with 1M NaCl, dialyzed against 1M acetic acid, and lyophilized. The lyophilized samples are dissolved in 0.8M NaCl-0.01M sodium phosphate buffer (pH 7.4) and passed through a 1.2×40 cm column of CM-Sephadex C-50 equilibrated with the buffer. PDGF is then eluted with a NaCl gradient (0.08 to 1M).

The active fractions are combined, dialyzed against 1M acetic acid, lyophilized, and dissolved in a small volume of 1M acetic acid. 0.5 ml portions are applied to a 1.2×100 cm column of Biogel P-150 (100 to 200 mesh) equilibrated with 1M acetic acid. The PDGF is then eluted with 1M acetic acid while 2 ml fractions are collected.

Each active fraction containing 100 to 200 mg of protein is lyophilized, dissolved in 100 ml of 0.4% trifluoroacetic acid, and subjected to reverse phase high performance liquid chromatography on a phenyl Bon-

dapak column (Waters). Elution with a linear acetonitrile gradient (0 to 60%) yields pure PDGF.

PDGF made by recombinant DNA technology can be prepared as follows:

Platelet-derived growth factor (PDGF) derived from human platelets contains two polypeptide sequences (PDGF-1 and PDGF-2 polypeptides; Antoniades, H.N. and Hunkapiller, M. (1983) Science 220:963-965). PDGF-1 is encoded by a gene localized in chromosome 7 (Betsholtz, C. et al., Nature 320:695-699), and PDGF-2 is encoded by the sis oncogene (Doolittle, R. et al. (1983) Science 221:275-277) localized in chromosome 22 (Dalla-Favera, R. (1982) Science 218:686-688). The sis gene encodes the transforming protein of the Simian Sarcoma Virus (SSV) which is closely related to PDGF-2 polypeptide. The human cellular c-sis also encodes the PDGF-2 chain (Rao, C.D. et al. (1986) Proc. Natl. Acad. Sci. USA 83:2392-2396). Because the two polypeptide chains of PDGF are coded by two different genes localized in separate chromosomes, the possibility exists that human PDGF consists of a disulfide-linked heterodimer of PDGF-1 and PDGF-2, or a mixture of the two homodimers (homodimer of PDGF-1 and homodimer of PDGF-2), or a mixture of the heterodimer and the two homodimers.

Mammalian cells in culture infected with the Simian Sarcoma Virus, which contains the gene encoding the PDGF-2 chain, were shown to synthesize the PDGF-2 polypeptide and to process it into a disulfide-linked homodimer (Robbins et al. (1983) Nature 305:605-608). In addition, PDGF-2 homodimer reacts with antisera raised against human PDGF. Furthermore, the functional properties of the secreted PDGF-2 homodimer are similar to those of platelet-derived PDGF in that it stimulates DNA synthesis in cultured fibroblasts, it induces phosphorylation at the tyrosino residue of a 185 kd cell membrane protein, and it is capable of competing with human (^{125}I)-PDGF for binding to specific cell surface PDGF receptors (Owen, A. et al. (1984) Science 225:54-56). Similar properties were shown for the sis/PDGF-2 gene product derived from cultured normal human cells (for example, human arterial endothelial cells), or from human malignant cells expressing the sis/PDGF-2 gene (Antoniades, H. et al. (1985) Cancer Cells 3:145-151).

The recombinant PDGF-2 homodimer is obtained by the introduction of cDNA clones of c-sis/PDGF-2 gene into mouse cells using an expression vector. The c-sis/PDGF-2 clone used for the expression was obtained from normal human cultured endothelial cells (Collins, T., et al. (1985) Nature 216:748-750).

PERIODONTAL AND BONE REGENERATION

To determine the effectiveness of PDGF in promoting periodontium and bone growth, the following experiments were performed.

Six year old beagle dogs (Laboratory Research Enterprises, Kalamazoo, Mich.) with naturally occurring periodontal disease were selected on the basis of an initial radiographic examination of their teeth. Teeth which exhibited 20% to 80% reduction of surrounding jaw bone were initially scaled using ultrasonic instruments. Referring to FIG. 1, an example of such reduction is shown, where a diseased jaw bone 10 (the extent of a normal bone is shown by dashed line 12) exhibits about 20% reduction in size due to the disease. A conventional gingival full thickness surgical flap 18 is then produced by an incision, shown at arrow 14, and 16. This removes gingiva 20 from around jaw bone 10 and tooth 24. Root 26 of the tooth is then planed to remove bacterial plaque and calculus. The experimental teeth were treated by the topical application of 500 ng to 5 mg, but generally one microgram of purified PDGF per tooth in a pharmacuetically acceptable carrier substance, e.g., a commercially available inert gel such as methyl cellulose, as shown by arrow 30. Generally, the PDGF is applied to the root of the tooth at the point where the cementum has been planed. It is thus near or adjacent cementum 32, bone 10, and interposed periodontal ligament (not shown). The remaining teeth received the carrier alone. The gingival flap was then placed back to near its original position and held together by a suture 32. The position of the PDGF-containing methyl cellulose is shown by shaded area 35.

Block biopsies of the teeth and surrounding bone were taken at two weeks post-treatment and prepared for histologic evaluation using standard demineralizing (10% trifluoroacetic acid) and processing techniques. Sections were stained with hematoxylin and eosin to allow old and new bone cementum and periodontal ligament to be differentiated.

RESULTS

Results of histologic analyses of periodontal and bone specimens indicated that, in PDGF-treated specimens: a) new bone was formed adjacent the root surfaces, b) a deposit resembling cementum was formed on the root surface adjacent the new bone, c) new bone was also formed on the periosteal and endosteal surfaces of the specimens, —d) evidence of ankylosis (fusion of bone and root surfaces) due to bone growth was present within the apical extent of the periodontal ligament, e) a dense layer of osteoblasts lined the newly formed bone, f) some osteoblasts were incorporated into the forming bone and formed osteocytes, g) a dense band of osteoblast-like cells was present within the connective tissue immediately coronal to the area of newly forming bone, and h) newly formed collagen fibers were observed inserting into the newly formed cementum deposits on the root surface. Thus, in treated sites, periodontal regeneration was occurring, including reformation of bone, connective tissue (periodontal ligament), and cementum.

In the control specimens there was no evidence of new bone formation, and there was an absence of new cementum-like deposits. Gingival connective tissue immediately coronal to the alveolar bone was oriented perpendicular to the bony surface appearing to form a "cap" over the original bone. There was no sign of any periodontal regeneration occurring. This is the first time that a purified polypeptide growth or differentiation factor, such as PDGF, has been demonstrated to enhance periodontal regeneration. These results indicate that the composition of the invention enhances osteogenic, cementogenic, and connective tissue responses.

USE

PDGF alone or in combination with other growth factors is useful for promoting bone healing, bone growth and regeneration or healing of the supporting structures of teeth injured by trauma or disease. It is also useful for promoting healing of a site of extraction of a tooth, for mandibular ridge augmentation, or at tooth implant sites. Bone healing would also be enhanced at sites of bone fracture or in infected areas, e.g., osteomy-

elitis, or at tumor sites. PDGF is also useful for promoting growth and healing of a ligament, e.g., the periodontal ligament, and of cementum.

In use, the PDGF or other growth or differentiation factor is applied directly to the area needing healing or regeneration. Generally, it is applied in a resorbable or non-resorbable carrier as a liquid or solid, and the site then covered with a bandage or nearby tissue. An amount sufficient to promote bone growth is generally between 500 ng and 5 mg for a 1 cm^2 area, but the upper limit is really one of for a 1 cm^2 area, but the upper limit is really one of expense of the PDGF, and is not a physiological limit.

Other embodiments are within the following claims.

We claim:

1. A method of promoting growth of damaged bone, periodontium, or ligament of a living mammal, comprising the steps of

producing a surgical flap of skin to expose said damaged bone, periodontium, or ligament,

planing said damaged bone or periodontium to remove organic matter from said bone or periodontium

applying platelet derived growth factor in a pharmaceutically acceptable carrier to said exposed bone, periodontium, or ligament,

replacing said flap, and

allowing said damaged bone, periodontium, or ligament to regrow.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,124,316

DATED : June 23, 1992

INVENTOR(S) : Harry N. Antoniades, et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1, line 26, change "heat-soluble protein" to --heat-stable protein--;

Column 2, line 11, correct the spelling of "cartilage";

Column 7, lines 11-12, delete the following: --for a 1 cm^2 area, but the upper limit is really one of--.

Signed and Sealed this

Sixteenth Day of November, 1993

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

2

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PATENT NUMBER	FEE AMT	SUR CHARGE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	STAT	ATTY DKT NUMBER
5,124,316	**$495.00**	**$0.00**	**07/582,332**	**06/23/92**	**09/13/90**	**04**	**NO**	**PAID**	**02854/015002**

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5,124,316	**$1,900.00**	**$0.00**	**07/582,332**	**06/23/92**	**09/13/90**	**08**	**NO**	**PAID**	**02854/015002**

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5,124,316	**$3,220.00**	**$0.00**	**07/582,332**	**06/23/92**	**09/13/90**	**12**	**NO**	**PAID**	**02854/015002**

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Alexandria, VA 22313-1450

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,124,316

DATED : June 23, 1992

INVENTOR(S) : Harry N. Antoniades, et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1, line 26, change "heat-soluble protein" to --heat-stable protein--;

Column 2, line 11, correct the spelling of "cartilage";

Column 7, lines 11-12, delete the following: --for a 1 cm^2 area, but the upper limit is really one of--.

Signed and Sealed this

Sixteenth Day of November, 1993

Attest:

Attesting Officer

BRUCE LEHMAN

Commissioner of Patents and Trademarks

4

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

TO: PAUL T. CLARK
FISH & RICHARDSON
STE 2500
ONE FINANCIAL CENTER
BOSTON, MA 02111-2658

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME NUMBER REFERENCED BELOW. A DIGEST OF THE DOCUMENT HAS ALSO BEEN MADE AND APPEARS IN THE OFFICE'S RECORDS AS SHOWN:

ASSIGNOR: 001 LYNCH, SAMUEL E. DOC DATE: 02/17/89

RECORDATION DATE: 02/27/89 NUMBER OF PAGES 001 REEL/FRAME 5027/0089

DIGEST: ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE: 501 PRESIDENT AND FELLOWS OF HARVARD COLLEGE, THE, CAMBRIDGE, MA., A MA. CORP.

SERIAL NUMBER 7-299763 FILING DATE 01/23/89
PATENT NUMBER ISSUE DATE 00/00/00

TITLE OF INVENTION: WOUND HEALING

INVENTOR: 001 ANTONIADES, HARRY N.
INVENTOR: 002 LYNCH, SAMUEL E.

ASSIGNMENT

For valuable consideration, I, Samuel (FIRST) E. (MIDDLE INITIAL) Lynch (LAST)

of Jamaica Plain (CITY OR TOWN), Massachusetts (STATE) hereby assign

to THE PRESIDENT AND FELLOWS OF HARVARD COLLEGE, a

Massachusetts charitable corporation having a place of business

at Cambridge, Massachusetts,

and its successors and assigns (collectively hereinafter called "the Assignee"), the entire right, title and interest throughout the world in the inventions and improvements which are the subject of an application for United States ~~Patent signed herewith~~ Serial No. 299,763 filed January 20, 1989 ~~this day~~, entitled WOUND HEALING

this assignment including said application, any and all United States and foreign patents granted for any of said inventions or improvements, and the right to claim priority based on the filing date of said application under the International Convention for the Protection of Industrial Property, the Patent Cooperation Treaty, the European Patent Convention, and all other treaties of like purposes; and I authorize the Assignee to apply in all countries in my name or in its own name for patents and like rights of exclusion and for inventor's certificates for said inventions and improvements; and I agree for myself and my heirs, legal representatives and assigns, without further compensation to perform such lawful acts and to sign such further applications, assignments, Preliminary Statements and other lawful documents as the Assignee may reasonably request to effectuate fully this assignment.

In Witness Whereof, I hereto set my hand and seal at Boston, Massachusetts, this 17 day of February, 1989.

/s/ Samuel E. Lynch L.S.

FIRST Samuel MIDDLE INITIAL E. LAST Lynch

State of Massachusetts :
ss.
County of Suffolk :

Before me this 17 day of February, 19 89, personally appeared Samuel E. Lynch known to me to be the person whose name is subscribed to the foregoing Assignment and acknowledged that he executed the same as his free act and deed for the purposes therein contained.

/s/ Deborah A. Mackenzie
Notary Public

[Notary's seal here]

RECORDED
PATENT & TRADEMARK OFFICE
FEB 27 89

My commission expires: Nov. 16, 1995

COMMISSIONER OF PATENTS
AND TRADEMARKS

REEL 5027 FRAME 0069

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

TO: PAUL T. CLARK
FISH & RICHARDSON
STE 2500
ONE FINANCIAL CENTER
BOSTON, MA 02111-2658

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME NUMBER REFERENCED BELOW. A DIGEST OF THE DOCUMENT HAS ALSO BEEN MADE AND APPEARS IN THE OFFICE'S RECORDS AS SHOWN:

ASSIGNOR: 001 ANTONIADES, HARRY N. DOC DATE: 02/17/89

RECORDATION DATE: 02/27/89 NUMBER OF PAGES 001 REEL/FRAME 5027/0090

DIGEST: ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE: 501 INSTITUTE OF MOLECULAR BIOLOGY, THE, BOSTON, MA., A DE. CORP.

SERIAL NUMBER 7-299763 FILING DATE 01/23/89
PATENT NUMBER ISSUE DATE 00/00/00

TITLE OF INVENTION: WOUND HEALING

INVENTOR: 001 ANTONIADES, HARRY N.
INVENTOR: 002 LYNCH, SAMUEL E.

ASSIGNMENT

For valuable consideration, I, Harry (FIRST) N. (MIDDLE INITIAL) Antoniades (LAST)

of Newton (CITY OR TOWN), Massachusetts (STATE) hereby assign

to THE INSTITUTE OF MOLECULAR BIOLOGY, Inc., a

Delaware corporation having a place of business

at Boston, Massachusetts,

and its successors and assigns (collectively hereinafter called "the Assignee"), the entire right, title and interest throughout the world in the inventions and improvements which are the subject of an application for United States ~~Patent signed herewith~~ Serial No. 299,763 filed January 20, 1989 ~~this day~~, entitled WOUND HEALING

this assignment including said application, any and all United States and foreign patents granted for any of said inventions or improvements, and the right to claim priority based on the filing date of said application under the International Convention for the Protection of Industrial Property, the Patent Cooperation Treaty, the European Patent Convention, and all other treaties of like purposes; and I authorize the Assignee to apply in all countries in my name or in its own name for patents and like rights of exclusion and for inventor's certificates for said inventions and improvements; and I agree for myself and my heirs, legal representatives and assigns, without further compensation to perform such lawful acts and to sign such further applications, assignments, Preliminary Statements and other lawful documents as the Assignee may reasonably request to effectuate fully this assignment.

In Witness Whereof, I hereto set my hand and seal at Boston, Massachusetts, this 17 day of February, 1989.

Harry N. Antoniades L.S.
(FIRST) Harry (MIDDLE INITIAL) N. (LAST) Antoniades

State of Massachusetts :
ss.
County of Suffolk :

Before me this 17 day of February, 1989, personally appeared Harry N. Antoniades known to me to be the person whose name is subscribed to the foregoing Assignment and acknowledged that he executed the same as his free act and deed for the purposes therein contained.

Deborah C. McKenzie
Notary Public

[Notary's seal here]

My commission expires: Nov 16, 1995

RECORDED
PATENT & TRADEMARK OFFICE
FEB 27 89

COMMISSIONER OF PATENTS

REEL 5027 FRAME 090

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ASSIGNMENT

For valuable consideration, we,

Full Name of Assignor	City	State (and Country if not USA)
Institute of Molecular Biology, Inc.	Delaware	P.O. Box 4278 Shrewsbury, MA 01545

hereby assign to

Full Name of Assignee	State of Incorporation	Business Address
BioMimetic Therapeutics, Inc.	Delaware	389 Nichol Mill Lane Franklin, TN 37067

and to its successors and assigns (collectively hereinafter called "the Assignee"), the entire right, title, and interest throughout the world in the inventions and improvements which are the subject of one or more of the patents and applications listed on Schedule A, which is attached hereto.

This assignment includes the patents and applications listed in the attached Schedule A, any and all United States and foreign patents, utility models, and design registrations granted for any of said inventions or improvements, and the right to claim priority based on the filing date of any of the patents and applications listed in the attached Schedule A under the International Convention for the Protection of Industrial Property, the Patent Cooperation Treaty, the European Patent Convention, and all other treaties of like purposes; and we authorize the Assignee to apply in all countries in our names or in its own name for patents, utility models, design registrations, and like rights of exclusion, and for inventors' certificates for said inventions and improvements; and we agree for ourselves and our respective heirs, legal representatives and assigns, without further compensation, to perform such lawful acts and to sign such further applications, assignments, Preliminary Statements, and other lawful documents as the Assignee may reasonably request to effectuate fully this assignment.

IN WITNESS WHEREOF, I hereto set my hand and seal at SHREWSBURY, MASSACHUSETTS, this 4th day of November, 2005

John M. Naples L.S.

John M. Naples, President
Institute of Molecular Biology, Inc.

STATE OF MASSACHUSETTS :

:ss.

COUNTY OF WORCESTER :

Before me this 4th day of November, 2005, before me, the undersigned notary public, personally appeared John M. Naples, proved to me through satisfactory evidence of identification, which consisted of MASSACHUSETTS DRIVERS LICENSE, to be the person whose name is subscribed to the foregoing Assignment, and acknowledged that he executed the same as his free act and deed for the purposes therein contained.

Notary Public

My Commission Expires: 02/07/08

[Notary's Seal Here]

PATRICIA MacISAAC
Notary Public
Commonwealth of Massachusetts
My Commission Expires
February 7, 2008

Schedule A
(Page 1 of 5)

C&E Ref No.	Status	Title	Application No.	Filed	Patent No.	Issued
02854-007001	Abandoned	WOUND HEALING AND BONE REGENERATION	06/930,762	14-Nov-1986		
02854-009001	Issued	WOUND HEALING AND BONE REGENERATION USING PDGF AND IGF-1	07/120,943	16-Nov-1987	4,861,757	29-Aug-1989
02854-010001	Issued	WOUND HEALING COMPOSITION OF TGF-ALPHA AND PDGF	07/136,399	22-Dec-1987	4,874,746	17-Oct-1989
02854-011001	Issued	WOUND HEALING USING IGF-I AND TGFβ	07/196,975	20-May-1988	4,983,581	8-Jan-1991
02854-011002	Abandoned	WOUND HEALING USING IGF-I AND TGFβ	07/530,649	30-May-1990		
02854-011003	Issued	WOUND HEALING USING IGF-II AND TGF	07/857,713	25-Mar-1992	5,256,644	26-Oct-1993
02854-012001	Issued	PROCESS OF WOUND HEALING USING PDGF AND EGF	07/231,145	10-Aug-1988	5,034,375	23-Jul-1991
02854-013003	Abandoned	WOUND HEALING	07/449,303	5-Dec-1989		
02854-013004	Abandoned	WOUND HEALING	07/639,060,303	9-Jan-1991		
02854-014001	Issued	WOUND HEALING USING PDGF AND IGF-II	07/272,090	16-Nov-1988	5,019,559	28-May-1991
02854-015001	Abandoned	WOUND HEALING	07/299,763	23-Jan-1989		
02854-015002	Issued	METHOD OF PERIDONTAL REGENERATION	07/582,332	13-Sep-1990	5,124,316	23-Jun-1992
02854-016001	Issued	WOUND HEALING COMPOSITION OF IL-1 AND PDGF OR IGF-1	07/403,969	7-Sep-1989	5,035,887	30-Jul-1991
02854-026001	Abandoned	BONE REGENERATION	07/799,375	27-Nov-1991		
02854-027001	Issued	NERVE REGENERATION	08/198,542	18-Feb-1994	6,506,727	14-Jan-2003
02854-033001	Issued	DEVICE TO PROMOTE DRUG-INDUCED NERVE REGENERATION	08/187,210	26-Jan-1994	5,656,605	12-Aug-1997
02854-034001	Issued	PYRIDINOLINE CROSSLINKS AS MARKERS OF PERIODONTAL AND PERI-IMPLANT DISEASE ACTIVITY	08/197,131	16-Feb-1994	5,516,699	14-May-1996

Schedule A
(Page 2 of 5)

C&I Ref No.	Country	Type	Status	Application No.	Filed	Patent No.	Issued
WOUND HEALING AND BONE REGENERATION							
02854-007AT1	Austria	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007AU1	Australia	PCT	Granted	83289/87	13-Nov-1987	600069	02-Aug-1990
02854-007BE1	Belgium	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007CA1	Canada	PCT	Granted	551,909	16-Nov-1987	1,322,714	05-Oct-1993
02854-007CH1	Switzerland	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007CN1	China	PCT	Granted	87101250.2	14-Nov-1987	87101250.2	30-Oct-1994
02854-007DE1	Germany	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007DK1	Denmark	PCT	Granted	3932/88	13-Nov-1987	25-Jul-81	30-May-05
02854-007EP1	Europe	PCT	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007FR1	France	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007FR2	France	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-007GB1	Great Britain	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007IE1	Ireland	PCT	Granted	3075/87	13-Nov-1987	60517	20-Jul-1994
02854-007IT1	Italy	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007JP1	Japan	PCT	Granted	500179/87	13-Nov-1987	1868245	26-Aug-1994
02854-007KR1	Korea	PCT	Granted	88-700829	13-Nov-1987	106280	17-Oct-1996
02854-007LU1	Luxembourg	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007NL1	Netherlands	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007NZ1	New Zealand	PCT	Granted	222551	16-Nov-1987	222551	
02854-007SE1	Sweden	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007TW1	Taiwan	PCT	Granted	76107672	15-Dec-1987	NI-51493	30-Jan-1992
02854-007ZA1	South Africa	PCT	Granted	87/8566	16-Nov-1987	87/8566	26-Jul-1989
02854-007OA1	Africa (OAPI)	PCT	Abandoned	PV59385	13-Nov-1987	9159	31-Mar-1992
02854-007MX1	Mexico	PCT	Abandoned	930672	16-Nov-1987	170454	23-Aug-1993
02854-007NO1	Norway	PCT	Abandoned	88/3127	13-Nov-1987		
02854-007WO1	International	PCT	Expired	PCT/US87/02975	13-Nov-1987		
WOUND HEALING							
02854-010AT1	Austria	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010AU1	Australia	PCT	Granted	37472/89	20-Dec-1988	613776	03-Dec-1991
02854-010BE1	Belgium	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010CA1	Canada	PCT	Granted	586,562	21-Dec-1988	1,322,164	14-Sep-1993
02854-010CH1	Switzerland	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010CN1	China	PCT	Granted	88109273.8	21-Dec-1988	88109273.8	19-Jul-1994
02854-010DE1	Germany	EPC	Granted	89901681.0	20-Dec-1988	P3885300.0	27-Oct-1993
02854-010DK1	Denmark	PCT	Granted	4122/89	20-Dec-1988	175947	08-Aug-2005
02854-010EP1	Europe	PCT	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010FR1	France	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010GB1	Great Britain	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010IE1	Ireland	PCT	Granted	3833/88	21-Dec-1988	61283	14-Oct-1994
02854-010IT1	Italy	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010JP1	Japan	PCT	Granted	501944/89	20-Dec-1988	1923551	25-Apr-1995
02854-010LU1	Luxembourg	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010MX1	Mexico	PCT	Granted	14307	22-Dec-1988	164966	09-Oct-1992
02854-010NL1	Netherlands	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010NZ1	New Zealand	PCT	Granted	227429	21-Dec-1988	227429	14-May-1991
02854-010SE1	Sweden	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010TW1	Taiwan	PCT	Granted	78100693	01-Feb-1989	NI-51930	20-Feb-1992
02854-010ZA1	South Africa	PCT	Granted	88/9594	22-Dec-1988	88/9594	27-Sep-1989
02854-010OA1	Africa (OAPI)	PCT	Abandoned	PV59630	20-Dec-1988	9129	31-Oct-1991
02854-010KR1	Korea	PCT	Abandoned	89/701555	20-Dec-1988		
02854-010NO1	Norway	PCT	Abandoned	89/3346	20-Dec-1988		
02854-010RU1	Russian Federation	PCT	Abandoned	4742130.14	20-Dec-1988		
02854-010WO1	International	PCT	Expired	PCT/US88/04557	20-Dec-1988		

Schedule A
(Page 3 of 5)

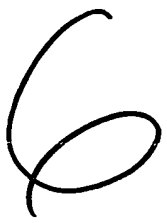
C & E Ref. No.	Country	Type	Status	Application No.	Filed	Patent No.	Issued
WOUND HEALING							
02854-011AT1	Austria	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011AT2	Austria	EPC	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011BE1	Belgium	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011BE2	Belgium	EPC	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011CA2	Canada	PCT	Granted	2,082,420	30-May-1991	2082420	20-Jul-2004
02854-011CH1	Switzerland	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011CH2	Switzerland	EPC	Granted	91910904.1	30-May-1991	531425	14-Aug-2002
02854-011DE1	Germany	EPC	Granted	89906917.3	22-May-1989	P68917300.8	03-Aug-1994
02854-011DE2	Germany	EPC	Granted	69133087.5	30-May-1991	0531425	14-Aug-2002
02854-011DK2	Denmark	EPC	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011EP1	Europe	PCT	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011EP2	Europe	PCT	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011ES2	Spain	EPC	Granted	0531425	30-May-1991	0531425	14-Aug-2002
02854-011FR1	France	EPC	Granted	0419534	22-May-1989	0419534	03-Aug-1994
02854-011FR2	France	EPC	Granted	0531425	30-May-1991	0531425	14-Aug-2002
02854-011GB1	Great Britain	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011GB2	Great Britain	EPC	Granted	0531425	30-May-1991	0531425	14-Aug-2002
02854-011GR2	Greece	EPC	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011IT1	Italy	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011IT2	Italy	EPC	Granted	0531425	30-May-1991	0531425	14-Aug-2002
02854-011JP1	Japan	PCT	Granted	506485/89	22-May-1989	1924479	25-Apr-1995
02854-011JP2	Japan	PCT	Granted	3-510861	30-May-1991	3,377,524	06-Dec-2002
02854-011LI2	Liechtenstein	EPC	Granted	91910904.1	30-May-1991	531425	14-Aug-2002
02854-011LU1	Luxembourg	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011LU2	Luxembourg	EPC	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011NL1	Netherlands	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011NL2	Netherlands	EPC	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011SE1	Sweden	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011SE2	Sweden	EPC	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011ES1	Spain	PCT	Abandoned	531425	30-May-1991		
02854-011WO1	International	PCT	Expired	PCT/US89/02229	22-May-1989		
02854-011WO2	International	PCT	Expired	PCT/US91/03829	30-May-1991		
WOUND HEALING							
02854-012AT1	Austria	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012BE1	Belgium	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012CA1	Canada	PCT	Granted	607,968	10-Aug-1989	1336816	29-Aug-1995
02854-012CH1	Switzerland	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012DE1	Denmark	EPC	Granted	89910545.6	10-Aug-1989	P68912758	26-Jan-1994
02854-012DE1	Germany	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012EP1	Europe	PCT	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012FR1	France	EPC	Granted	89910545.6	10-Aug-1989	382841	26-Jan-1994
02854-012GB1	Great Britain	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012IT1	Italy	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012JP1	Japan	PCT	Granted	509811/89	10-Aug-1989	1975393	27-Sep-1995
02854-012LU1	Luxembourg	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012NL1	Netherlands	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012SE1	Sweden	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012WO1	International	PCT	Expired	PCT/US89/03490	10-Aug-1989		

Schedule A
(Page 4 of 5)

C & E Ref. No.	Country	Type	Status	Application No.	Filed	Patent No.	Issued
WOUND HEALING USING PDGF AND IGF-II							
02854-014AT1	Austria	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014BE1	Belgium	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014CA1	Canada	PCT	Granted	2,060,208	10-Apr-1990	2,060,208	20-Feb-2001
02854-014CH1	Switzerland	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014DE1	Germany	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014DK1	Denmark	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014EP1	Europe	PCT	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014ES1	Spain	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014FR1	France	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014GB1	Great Britain	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014IT1	Italy	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014JP1	Japan	PCT	Granted	507475/90	10-Apr-1990	2030420	19-Mar-1996
02854-014LU1	Luxembourg	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014NL1	Netherlands	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014SE1	Sweden	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014WO1	International	PCT	Expired	PCT/US90/01936	10-Apr-1990		
WOUND HEALING							
02854-016CA1	**Canada**	**PCT**	**Pending**	**2,040,410**	**07-Sep-1990**		
02854-016JP1	Japan	PCT	Granted	2-512565	07-Sep-1990	1969836	18-Sep-1995
02854-016EP1	Europe	PCT	Abandoned	90913582.4	07-Sep-1990		
02854-016WO1	International	PCT	Expired	PCT/US90/05062	07-Sep-1990		
BONE REGENERATION							
02854-026CA1	Canada	PCT	Abandoned	2,123,803	24-Nov-1992		
02854-026JP1	Japan	PCT	Abandoned	Hei-05-510253	26-May-1994		
02854-026EP1	Europe	PCT	Abandoned	93900683.9	24-Nov-1992		
02854-026WO1	International	PCT	Expired	PCT/US92/10214	24-Nov-1992		
MEDICAMENT FOR PROMOTING GROWTH OF MAMMALIAN NERVE - IMB Only							
02854-027AU1	Australia	PCT	Granted	30668/92	04-Nov-1992	673659	12-Mar-1997
02854-027CA1	Canada	PCT	Granted	2,123,685	04-Nov-1992	2,123,685	07-Oct-2003
02854-027CH1	Switzerland	PCT	Granted	2309/93-2	04-Nov-1992	684573	31-Oct-1994
02854-027JP1	Japan	PCT	Allowed	5-510115	04-Nov-1992		
02854-027JP2	Japan	PCT	Pending	2005-292267	28-Sep-2005		
02854-027EP1	Europe	PCT	Abandoned	92924312.9	04-Nov-1992		
02854-027PL1	Poland	PCT	Abandoned	P303981	04-Nov-1992		
02854-027ZA1	South Africa	PCT	Abandoned		04-Nov-1992		
02854-027WO1	International	PCT	Expired	PCT/US92/09545	04-Nov-1992		

Schedule A
(Page 5 of 5)

C&E Ref. No.	Country	Type	Status	Application Nos.	Filed	Patent No.	Issued
A DEVICE TO PROMOTE DRUG-INDUCED NERVE REGENERATION							
02854-033WO1	International	PCT	Expired	PCT/US95/00985	25-Jan-1995		
PYRIDINOLINE CROSSLINKS AS MARKERS OF PERIODONTAL AND PERI-IMPLANT DISEASE ACTIVITY							
02854-034AT1	Austria	EPC	Granted	95909234.7	13-Jan-1995	E220458	10-Jul-2002
02854-034BE1	Belgium	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034CA1	**Canada**	**PCT**	**Pending**	**2,183,452**	**13-Jan-1995**		
02854-034CH1	Switzerland	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034DE1	Germany	EPC	Granted	95909234.7	13-Jan-1995	69527350.7	10-Jul-2002
02854-034DK1	Denmark	PCT	Granted	95909234.7	13-Jan-1995	0745221	07-Oct-2002
02854-034EP1	Europe	PCT	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034ES1	Spain	EPC	Granted	95909234.7	13-Jan-1995	ES2179867T3	10-Jul-2002
02854-034FR1	France	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034GB1	Great Britain	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034GR1	Greece	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034IE1	Ireland	PCT	Granted	95909234.7	13-Jan-1995	0745221	
02854-034IT1	Italy	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034JP1	Japan	PCT	Granted	7-521795	13-Jan-1995	3,521,913	20-Feb-2004
02854-034KP1	N. Korea	PCT	Granted	96-0594	16-Aug-1996	31,331	22-Jan-1998
02854-034NL1	Netherlands	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034PT1	Portugal	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034PT1	Sweden	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034CN1	China	PCT	Abandoned	95192443.5	13-Jan-1995		
02854-034KR1	S. Korea	PCT	Abandoned	1996-704491	16-Aug-1996		
02854-034WO1	International	PCT	Expired	PCT/US95/00509	13-Jan-1995		



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Mr. Mark Citron
Vice President
Biomimetic Pharmaceuticals, Incorporated
389-A Nichol Mill Lane
Franklin, Tennessee 37067

NOV 18 2005

Re: P040013
GEM 21S (Growth-factor Enhanced Matrix)
Filed: March 14, 2004
Amended: March 25, April 9, 14, July 7,8,26,28, August 4, September 3,14,22, October 7,12,13,28, November 3, 2004 February 3,4,14,16, March 2,3,7,8,18,25, April 4,14,25, May 18, July 14,15, August 8,9, 18, 31, September 21, 26 and October 7, 2005.
Procode: NPZ

Dear Mr. Citron:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the GEM 21S (Growth-factor Enhanced Matrix). This device is indicated to treat the following periodontally related defects:

- Intrabony periodontal defects
- Furcation periodontal defects
- Gingival recession associated with periodontal defects.

We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions described below and in the "Conditions of Approval" (enclosed).

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that, to ensure the safe and effective use of the device, the device is further restricted within the meaning of section 520(e) under the authority of section 15(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

In addition to the postapproval requirements outlined in the enclosure, you have agreed to

- establish, and validate an immunological identity test for rhPDGF-BB received from the manufacturer. The information will be submitted as a supplement for FDA review by June 1, 2006. Following review and approval by the FDA, the new assay

will replace SDS-PAGE as an identity test for the incoming bulk drug substance.

- evaluate the historical release and stability specifications for GEM21S following manufacturing of 30 lots of product and submit the results as a report to the PMA with any proposed changes by September 1, 2006. Any proposal to broaden or shift the specifications should be submitted as a supplement to the premarket approval application.
- not use lots of PDGF drug substance for manufacture of GEM 21S which was fermented after September, 2002 until supplemental approval is received from FDA to include the PDGF fermentation site.

Expiration dating for this device has been established and approved at 18 months.

Please be aware that changing reference standards will change the potency specification, so a supplement must be submitted with each change to a reference standard. We suggest you send the details of the protocol for qualification and expiration dating of new reference standards to us for review before starting any of the testing.

CDRH does not evaluate information related to contract liability warranties, however you should be aware that any such warranty statements must be truthful, accurate, and not misleading, and must be consistent with applicable Federal and State laws.

CDRH will notify the public of its decision to approve your PMA by making available a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at http://www.fda.gov/cdrh/pmapage.html. Written requests for this information can also be made to the Dockets Management Branch, (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with any postapproval requirement constitutes a ground for withdrawal of approval of a PMA. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. The labeling will not routinely be reviewed by FDA staff when PMA applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form.

If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Ms. Angela Blackwell at (301) 827-5283.

Sincerely yours,

Donna-Bea Tillman Ph.D., M.P.A.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Last Modified: 1-31-02

CONDITIONS OF APPROVAL

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e) or (f). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations that require a PMA supplement cannot be briefly summarized; therefore, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report (see below). FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

Alternate submissions permitted under 21 CFR 814.39(f) for manufacturing process changes include the use of a 30-day Notice. The manufacturer may distribute the device 30 days after the date on which the FDA receives the 30-day Notice, unless the FDA notifies the applicant within 30 days from receipt of the notice that the notice is not adequate.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

1. Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

2. Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

   a. unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

   b. reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

1. A mix-up of the device or its labeling with another article.

2. Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and:

   a. has not been addressed by the device's labeling; or

   b. has been addressed by the device's labeling but is occurring with unexpected severity or frequency.

3. Any significant chemical, physical or other change or deterioration in the device, or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION.
The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984. This regulation was replaced by the reporting requirements of the Safe Medical Devices Act of 1990 which became effective July 31, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to the FDA whenever they receive or otherwise become aware of information, from any source, that reasonably suggests that a device marketed by the manufacturer or importer:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for a PMA, the manufacturer shall submit the appropriate reports required by the MDR Regulation within the time frames as identified in 21 CFR 803.10(c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health. The manufacturer is responsible for submitting a baseline report on FDA Form 3417 for a device when the device model is first reported under 21 CFR 803.50. This baseline report is to include the PMA reference number. Any written report and its envelope is to be specifically identified, e.g., "Manufacturer Report," "5-Day Report," "Baseline Report," etc.

Any written report is to be submitted to:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
PO Box 3002
Rockville, Maryland 20847-3002

Copies of the MDR Regulation (FOD # 336&1336) and FDA publications entitled "An Overview of the Medical Device Reporting Regulation" (FOD # 509) and "Medical Device Reporting for Manufacturers" (FOD #987) are available on the CDRH WWW Home Page. They are also available through CDRH's Fact-On-Demand (F-O-D) at 800-899-0381. Written requests for information can be made by sending a facsimile to CDRH's Division of Small Manufacturers International and Consumer Assistance (DSMICA) at 301-443-8818.

7

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Our Reference No. 96-1408

December 16, 1997

Ms. Joan F. Roelands
OMJ Pharmaceuticals, Inc.
Carr. #2, Km 45.6
Bo. Campo Alegre
Manati, Puerto Rico 00674

Dear Ms. Roelands:

Your biologics license application for Becaplermin is approved effective this date. OMJ Pharmaceuticals, Inc., Manati, Puerto Rico, is hereby authorized to manufacture and ship for sale, barter, or exchange in interstate and foreign commerce Becaplermin under Department of Health and Human Services Biologics License No. 1196.

Becaplermin is indicated for treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond, and have adequate blood supply.

Under this authorization, you are approved to manufacture Becaplermin utilizing Becaplermin Concentrate manufactured by Chiron Corporation (Biologics License No. 1106) under a shared manufacturing arrangement. Any addition or deletion of establishments involved in the shared manufacturing arrangement will require the submission of appropriate supporting data in order to ensure continued compliance with the approved standards for the manufacture of Becaplermin.

In accordance with approved labeling, your product will be distributed by McNeil Pharmaceutical under the tradename Regranex, and will be marketed as a gel formulation in 2, 7.5 and 15 gram fill sizes.

You are not currently required to submit samples of future lots of this product to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2. FDA will continue to monitor compliance with 21 CFR 610.1 requiring assay and release of only those lots that meet release specifications.

The dating period for this product shall be 9 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of formulation of the final gel product. Results of ongoing stability studies should be submitted throughout the dating period as they become available including the results of stability studies from the first three production lots.

We acknowledge your written commitments dated December 15, 1997 to:

1. Identify (in conjunction with RWJPRI) with due diligence the cause for the change in the stability profile observed with the finished drug product. After sufficient data are collected and analyzed, submit the conclusions of the investigation to the Agency.

2. Place [redacted] batches of Becaplermin on stability program at 5°C (2-8°C). Place at least one production batch per tube size on stability each month that particular tube size is manufactured from November, 1997 to September, 1998. If the 2, 7.5 and 15g tube sizes are all manufactured within the same month, then only the 2 and 15g tube sizes will be placed on stability to bracket the results.

(b)(4)

3. Continuously monitor the temperature of product shipments from OMJ Pharmaceuticals, Inc., [redacted] Puerto Rico, to the [redacted] Distribution Center, [redacted] [redacted] Real time, freeze/thaw, and accelerated temperature stability data will be collected from 3 lots of product to document the long term stability following temperature excursions. Until additional stability data are gathered, samples from any lot exposed to temperatures outside 2-8°C will not be commercially distributed without agency concurrence and if released, samples will be placed on a stability study.

(b)(4)

4. Validate shipping of stability samples sent to Chiron Corporation and to discard any samples exposed to temperatures outside of the specified range.

5. Manufacture a [redacted] lot of product for which the thawed drug substance was held for 18 days. This lot will be entered into the stability program.

(b)(4)

6. We also acknowledge additional information in your letter of December 15, 1997, addressing the agency's observations noted during the April 28 - May 7, 1997, preapproval inspection and your commitment to provide further information and data within the timelines specified.

7. In addition, we acknowledge your letter of December 11, 1997 in which you commit to submitting to CBER final reports of the clinical studies for Becaplermin in venous stasis and pressure ulcers.

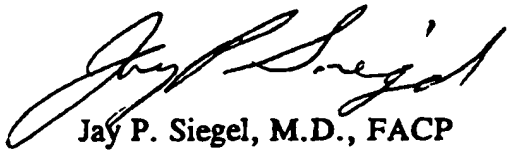
Any changes in the supplier of Becaplermin Concentrate, or in the manufacture, packaging or labeling of the product or in the manufacturing facilities will require the submission of information to your biologics license application for our review and written approval consistent with 21 CFR 601.12.

It is requested that adverse experience reports be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). All adverse experience

reports should be prominently identified according to 21 CFR 600.80 and be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

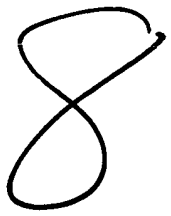
Please submit three copies of all final printed labeling at the time of use and include part II of the label transmittal form with completed implementation information. In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2567 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Staff, HFM-202, 1401 Rockville Pike, Rockville, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by an FDA Form 2567. All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other similar products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Sincerely yours,



Jay P. Siegel, M.D., FACP
Director
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

cc: Jacqueline Coelln/RWJPRI



REGRANEX® GEL 0.01%
(becaplermin)

DESCRIPTION

REGRANEX® Gel contains becaplermin, a recombinant human platelet-derived growth factor (rhPDGF-BB) for topical administration. Becaplermin is produced by recombinant DNA technology by insertion of the gene for the B chain of platelet-derived growth factor (PDGF) into the yeast, *Saccharomyces cerevisiae*. Becaplermin has a molecular weight of approximately 25 KD and is a homodimer composed of two identical polypeptide chains that are bound together by disulfide bonds. Becaplermin Concentrate is produced by Chiron Corp. and supplied to OMJ Pharmaceuticals under a shared manufacturing arrangement. REGRANEX Gel is a non-sterile, low bioburden, preserved, sodium carboxymethylcellulose-based (CMC) topical gel, containing the active ingredient becaplermin and the following inactive ingredients: sodium chloride, sodium acetate trihydrate, glacial acetic acid, water for injection, and methylparaben, propylparaben, and m-cresol as preservatives and l-lysine hydrochloride as a stabilizer. Each gram of REGRANEX Gel contains 100 µg of becaplermin.

CLINICAL PHARMACOLOGY

REGRANEX has biological activity similar to that of endogenous platelet-derived growth factor, which includes promoting the chemotactic recruitment and proliferation of cells involved in wound repair and enhancing the formation of granulation tissue.

Pharmacokinetics

Ten patients with Stage III or IV (as defined in the International Association of Enterostomal Therapy (IAET) guide to chronic wound staging, *J. Enterostomal Ther* 15:4, 1988 and *Decubitis* 2:24, 1969) lower extremity diabetic ulcers received topical applications of becaplermin gel 0.01% at a dose range of 0.32-2.95 µg/kg (7µg/cm²) daily for 14 days. Six patients had non-quantifiable PDGF levels at baseline and throughout the study, two patients had PDGF levels at baseline which did not increase substantially, and two patients had PDGF levels that increased sporadically above their baseline values during the 14 day study period.

Systemic bioavailability of becaplermin was less than 3% in rats with full thickness wounds receiving single or multiple (5 days) topical applications of 127 µg/kg (20.1 µg/cm² of wound area) of becaplermin gel.

Clinical Studies

The effects of REGRANEX Gel on the incidence of and time to complete healing in lower extremity diabetic ulcers were assessed in four randomized controlled studies. Of 922 patients studied, 478 received either REGRANEX Gel 0.003% or 0.01%. All study participants had lower extremity diabetic neuropathic ulcers that extended into the subcutaneous tissue or beyond (Stages III and IV of the IAET guide to chronic wound staging). Ninety-three percent of the patients enrolled in these four trials had foot ulcers. The remaining 7% of the patients had ankle or leg ulcers. The diabetic ulcers were of at least 8 weeks duration and had an adequate blood supply (defined as T_cpO_2 > 30 mm Hg). In the four trials, ninety-five percent of the ulcers measured in area up to 10 cm², and the median ulcer size at baseline ranged from 1.4 cm² to 3.5 cm². All treatment groups received a program of good ulcer care consisting of initial complete sharp debridement, a non-weight-bearing regimen, systemic treatment for wound-related infection if present, moist saline dressings changed twice a day, and additional debridement as necessary. REGRANEX Gel 0.003% or 0.01% or placebo gel was applied once a day and covered with a saline moistened dressing. After approximately 12 hours, the gel was gently rinsed off and a saline moistened dressing was then applied for the remainder of the day. Patients were treated until complete healing, or for a period of up to 20 weeks. Patients were considered a treatment failure if their ulcer did not show an approximately 30% reduction in initial ulcer area after eight to ten weeks of REGRANEX Gel therapy.

The primary endpoint, incidence of complete ulcer closure within 20 weeks, for all treatment arms is shown in Figure 1. In each study, REGRANEX Gel in conjunction with good ulcer care was compared to placebo gel plus good ulcer care or good ulcer care alone.

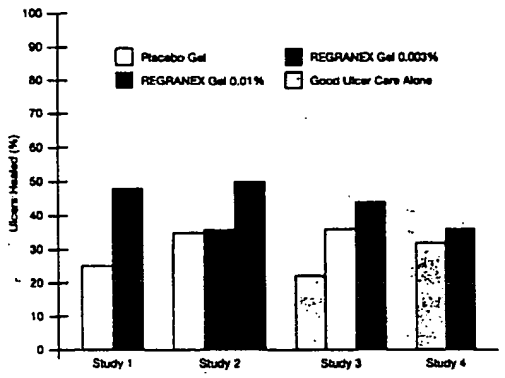
In Study 1, a multicenter, double-blind, placebo controlled trial of 118 patients, the incidence of complete ulcer closure for REGRANEX Gel 0.003% (n=61) was 48% versus 25% for placebo gel (n=57; p=0.02, logistic regression analysis).

In Study 2, a multicenter, double-blind, placebo controlled trial of 382 patients, the incidence of complete ulcer closure for REGRANEX Gel 0.01% (n=123), was 50% versus 36% for REGRANEX Gel 0.003% (n=132), and 35% for placebo gel (n=127). Only REGRANEX Gel 0.01% was significantly different from placebo gel (p=0.01, logistic regression analysis).

The primary goal of Study 3, a multicenter controlled trial of 172 patients, was to assess the safety of vehicle gel (placebo; n=70) compared to good ulcer care alone (n=68). The study included a small (n=34) REGRANEX Gel 0.01% arm. Incidences of complete ulcer closure were 44% for REGRANEX Gel, 35% for placebo gel and 22% for good ulcer care alone.

In Study 4, a multicenter, evaluator-blind, controlled trial of 250 patients, the incidences of complete ulcer closure in the REGRANEX Gel 0.01% arm (n=128) (36%) and good ulcer care alone (n=122) (32%) were not statistically different.

Figure 1: Incidence of Complete Healing



In general, where REGRANEX Gel was associated with higher incidences of complete ulcer closure, differences in the incidence first became apparent after approximately 10 weeks and increased with continued treatment (Table 1).

Table 1: Life Table Estimates of the Incidence (%) of Complete Healing Over Time for Study 2

	REGRANEX Gel 0.01% (%)	Placebo Gel (%)
Week 2	1	0
Week 4	8	2
Week 6	9	6
Week 8	16	14
Week 10	23	18
Week 12	34	25
Week 14	37	28
Week 16	43	33
Week 18	46	34
Week 20	50	37

In a 3-month follow-up period where no standardized regimen of preventative care was utilized, the incidence of ulcer recurrence was approximately 30% in all treatment groups, demonstrating that the durability of ulcer closure was comparable in all treatment groups.

The efficacy of REGRANEX Gel for the treatment of non-diabetic ulcers is under evaluation.

INDICATIONS AND USAGE

REGRANEX Gel is indicated for the treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. When used as an adjunct to, and not a substitute for, good ulcer care practices including initial sharp debridement, pressure relief and infection control, REGRANEX Gel increases the incidence of complete healing of diabetic ulcers.

The efficacy of REGRANEX Gel for the treatment of diabetic neuropathic ulcers that do not extend through the dermis into subcutaneous tissue (Stage I or II, IAET staging classification) or ischemic diabetic ulcers has not been evaluated.

CONTRAINDICATIONS

REGRANEX Gel is contraindicated in patients with:
- known hypersensitivity to any component of this product (e.g., parabens);
- known neoplasm(s) at the site(s) of application.

635-10-240-1

REGRANEX® GEL 0.01%
(becaplermin)

102401

WARNINGS
REGRANEX (becaplermin) Gel is a non-sterile, low bioburden preserved product. Therefore, it should not be used in wounds that close by primary intention.

PRECAUTIONS
For external use only.

If application site reactions occur, the possibility of sensitization or irritation caused by parabens or m-cresol should be considered.

The effects of becaplermin on exposed joints, tendons, ligaments, and bone have not been established in humans. In pre-clinical studies, rats injected at the metatarsals with 3 or 10 µg/site (approximately 60 or 200 µg/kg) of becaplermin every other day for 13 days displayed histological changes indicative of accelerated bone remodeling consisting of periosteal hyperplasia and subperiosteal bone resorption and exostosis. The soft tissue adjacent to the injection site had fibroplasia with accompanying mononuclear cell infiltration reflective of the ability of PDGF to stimulate connective tissue growth.

Information for Patients
Patients should be advised that:
- hands should be washed thoroughly before applying REGRANEX Gel;
- the tip of the tube should not come into contact with the ulcer or any other surface; the tube should be recapped tightly after each use;
- a cotton swab, tongue depressor, or other application aid should be used to apply REGRANEX Gel;
- REGRANEX Gel should only be applied once a day in a carefully measured quantity (see Dosage and Administration section). The measured quantity of gel should be spread evenly over the ulcerated area to yield a thin continuous layer of approximately ⅛ of an inch thickness. The measured length of the gel to be squeezed from the tube should be adjusted according to the size of the ulcer. The amount of REGRANEX Gel to be applied daily should be recalculated at weekly or biweekly intervals by the physician or wound care giver;

Step-by-step instructions for application of REGRANEX Gel are as follows:

- Squeeze the calculated length of gel on to a clean, firm, non-absorbable surface, e.g., wax paper.
- With a clean cotton swab, tongue depressor, or similar application aid, spread the measured REGRANEX Gel over the ulcer surface to obtain an even layer.
- Cover with a saline moistened gauze dressing.

- after approximately 12 hours, the ulcer should be gently rinsed with saline or water to remove residual gel and covered with a saline-moistened gauze dressing (without REGRANEX Gel);
- It is important to use REGRANEX Gel together with a good ulcer care program, including a strict non-weight-bearing program;
- excess application of REGRANEX Gel has not been shown to be beneficial;
- REGRANEX Gel should be stored in the refrigerator. Do not freeze REGRANEX Gel;
- REGRANEX Gel should not be used after the expiration date on the bottom, crimped end of the tube.

Drug Interactions
It is not known if REGRANEX Gel interacts with other topical medications applied to the ulcer site. The use of REGRANEX Gel with other topical drugs has not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Becaplermin was not genotoxic in a battery of *in vitro* assays, (including those for bacterial and mammalian cell point mutation, chromosomal aberration, and DNA damage/repair). Becaplermin was also not mutagenic in an *in vivo* assay for the induction of micronuclei in mouse bone marrow cells.

Carcinogenesis and reproductive toxicity studies have not been conducted with REGRANEX Gel.

Pregnancy: Category C
Animal reproduction studies have not been conducted with REGRANEX Gel. It is also not known whether REGRANEX Gel can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. REGRANEX Gel should be given to pregnant women only if clearly needed.

Nursing Mothers
It is not known whether becaplermin is excreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when REGRANEX Gel is administered to nursing women.

Pediatric Use
Safety and effectiveness of REGRANEX Gel in pediatric patients below the age of 16 years have not been established.

ADVERSE REACTIONS
Patients receiving REGRANEX Gel, placebo gel, and good ulcer care alone had a similar incidence of ulcer-related adverse events such as infection, cellulitis, or osteomyelitis. However, erythematous rashes occurred in 2% of patients treated with REGRANEX Gel and placebo, and none in patients receiving good ulcer care alone. The incidence of cardiovascular, respiratory, musculoskeletal and central and peripheral nervous system disorders was not different across all treatment groups. Mortality rates were also similar across all treatment groups. Patients treated with REGRANEX Gel did not develop neutralizing antibodies against becaplermin.

DOSAGE AND ADMINISTRATION
The amount of REGRANEX Gel to be applied will vary depending upon the size of the ulcer area. To calculate the length of gel to apply to the ulcer, measure the greatest length of the ulcer by the greatest width of the ulcer in either inches or centimeters. To calculate the length of gel in inches, use the formula shown below in Table 2, and to calculate the length of gel in centimeters, use the formula shown below in Table 3.

Table 2: Formula to Calculate Length of Gel in Inches to be Applied Daily

INCHES

Tube Size	Formula
15 or 7.5g tube	length X width X 0.6
2g tube	length X width X 1.3

Using the calculation, each square inch of ulcer surface will require approximately ½ inch length of gel squeezed from a 15g or 7.5g tube, or approximately 1½ inch length of the gel from a 2g tube. For example, if the ulcer measures 1 inch by 2 inches, then a 1¼ inch length of gel should be used for 15g or 7.5g tubes (1 X 2 X 0.6 = 1¼) and 2¾ inch gel length should be used for 2g tube (1 X 2 X 1.3 = 2¾).

Table 3: Formula to Calculate Length of Gel in Centimeters to be Applied Daily

CENTIMETERS

Tube Size	Formula
15 or 7.5g tube	length X width ÷ 4
2g tube	length X width ÷ 2

Using the calculations for ulcer size in centimeters, each square centimeter of ulcer surface will require approximately a 0.25 centimeter length of gel squeezed from a 15g or 7.5g tube, or approximately a 0.5 centimeter length of gel from a 2g tube. For example, if the ulcer measures 4 cm by 2 cm, then a 2 centimeter length of gel should be used for 15g or 7.5g tube [(4 X 2) ÷ 4 = 2] and a 4 centimeter length of gel should be used for 2g tube [(4 X 2) ÷ 2 = 4].

The amount of REGRANEX Gel to be applied should be recalculated by the physician or wound care giver at weekly or biweekly intervals depending on the rate of change in ulcer area. The weight of REGRANEX Gel from 7.5g and 15g tubes is 0.65g per inch length and 0.25g per centimeter length.

To apply REGRANEX Gel, the calculated length of gel should be squeezed on to a clean measuring surface, e.g., wax paper. The measured REGRANEX Gel is transferred from the clean measuring surface using an application aid and then spread over the entire ulcer area to yield a thin continuous layer of approximately ⅛ of an inch thickness. The site(s) of application should then be covered by a saline moistened dressing and left in place for approximately 12 hours. The dressing should then be removed and the ulcer rinsed with saline or water to remove residual gel and covered again with a second moist dressing (without REGRANEX Gel) for the remainder of the day. REGRANEX Gel should be applied once daily to the ulcer until complete healing has occurred. If the ulcer does not decrease in size by approximately 30% after 10 weeks of treatment or complete healing has not occurred in 20 weeks, continued treatment with REGRANEX Gel should be reassessed. The step-by-step instructions for applying REGRANEX Gel for home administration are described under "Information for Patients".

HOW SUPPLIED
REGRANEX (becaplermin) Gel, supplied as a clear, colorless to straw-colored preserved gel containing 100µg of becaplermin per gram of gel, is available in multi-use tubes in the following sizes:

2g tubes	NDC 0045-0810-02
7.5g tubes	NDC 0045-0810-07
15g tubes	NDC 0045-0810-15

REGRANEX Gel is for external use only.

Storage
Store refrigerated: 2-8°C (36-46°F). DO NOT FREEZE. DO NOT USE THE GEL AFTER THE EXPIRATION DATE AT THE BOTTOM OF THE TUBE.

Caution: Federal (USA) law prohibits dispensing without prescription.

U.S. Patent #5,457,093

McNEIL PHARMACEUTICAL

Distributed by:
McNEIL PHARMACEUTICAL
Raritan, New Jersey 08869

Manufactured by:
ONJ Pharmaceuticals, Inc.
U.S. License No. 1196
San German, Puerto Rico 00683

Becaplermin Concentrate provided by: Chiron Corp.,
U.S. License No. 1106, Emeryville, CA 94608

Issued January 1998

635-10-240-1

102401

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PATENT
Atty Ref. No. 273802801100

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

I hereby certify that this paper or fee is being deposited on February 13, 1998 with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. § 1.10 as Express Mail Label No. EM056839453US and is addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

2/13/98
Date

Robyn Leiner
Robyn Leiner

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Murray et al.

Patent No.: 4,845,075

Issued: July 4, 1989

For: BIOLOGICALLY ACTIVE B-CHAIN HOMODIMERS

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. SECTION 156

Commissioner for Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

Dear Sir:

In accordance with 35 U.S.C. Section 156, Applicant, ZymoGenetics, Inc., a corporation of the State of Washington, having a place of business at 1201 Eastlake Avenue East, Seattle, Washington, 98102, (hereinafter "Applicant") represents that it is the assignee of the entire interest in and to Letters Patent of the United States No. 4,845,075, granted to Mark Murray and James Kelly for BIOLOGICALLY ACTIVE B-CHAIN HOMODIMERS by virtue of an assignment in favor of ZymoGenetics, recorded on February 26, 1987, on Reel 4694, Frame 0991, and by virtue of an assignment for U.S. Patent Application No. 06/705,175, filed February 25, 1985, directed to

EXPRESSION OF BIOLOGICALLY ACTIVE PDGF ANALOGS IN EUCARYOTIC CELLS, recorded on October 21, 1985, on Reel 4469, Frame 0438.

Applicant, through undersigned counsel, hereby applies for a 4.36 year (1593 day) extension of the term of United States Patent No. 4,845,075 under 35 U.S.C. § 156 on the basis of the following information submitted in accordance with the provisions of Title 37 C.F.R. § 1.740(a)(1)-(17), set forth in the sequence of those subparagraphs. Filed herewith is a Certificate under 37 C.F.R. § 3.73(b) and a Power of Attorney authorizing the undersigned to file and prosecute this Application for Extension of Patent Term, and to transact all business in relations thereto (EXHIBIT 1).

(1) This application for extension is based upon the regulatory review period before the FDA for the approved products, "Becaplermin Concentrate" and "REGRANEX® Gel" (hereinafter "REGRANEX®"). REGRANEX® contains becaplermin, a recombinant human platelet-derived growth factor composed of two disulfide-linked B-chain polypeptides (rhPDGF-BB) for topical administration. Becaplermin Concentrate is produced by Chiron Corporation and supplied to OMJ Pharmaceuticals, Inc., an affiliate of Ortho-McNeil Pharmaceutical Corporation, a wholly owned subsidiary of Johnson & Johnson under a shared manufacturing agreement. Letters of authorization executed by the marketing applicants to the patent assignee are attached as EXHIBIT 2. REGRANEX®, is a non-sterile, low bioburden, preserved, sodium carboxymethylcellulose based (CMC) topical gel, containing the active ingredient becaplermin and the following inactive ingredients: sodium chloride, sodium acetate trihydrate, glacial acetic acid, water for injection, and methylparaben, propylparaben, and m-cresol as preservatives and l-lysine hydrochloride as a stabilizer. Each gram of REGRANEX® contains 100μg of becaplermin and is indicated for use in the treatment of diabetic ulcers as further described in attached EXHIBIT 3 (which is the package insert for this product).

(2) The approved products were subject to regulatory review under Public Health Service Act, Section 351 (42 U.S.C. § 262).

(3) The approved products, "Becaplermin Concentrate" (Biologics License No. 1106) and "REGRANEX®" (Biologics License No. 1196) received permission for commercial marketing or use after a regulatory review period under Public Health Service Act, Section 351 (42 U.S.C. § 262) on December 16, 1997.

(4) The active ingredient in "Becaplermin Concentrate" and "REGRANEX®" is a recombinant form of human platelet-derived growth factor composed of two disulfide-linked B chain polypeptides (rhPDGF-BB). To the best of Applicant's knowledge, the permission for the commercial marketing or use of this product after such regulatory review period is the first permitted commercial marketing or use of such product under the Public Health Service Act.

(5) This Application for extension of patent term under 35 U.S.C. Section 156, is being submitted within the permitted 60 day period, which period will expire on February 13, 1998.

(6) The complete identification of the patent for which extension is being sought is as follows:

U.S. Patent No.:	4,845,075
Issue Date:	July 4, 1989
Expires:	July 4, 2006
Inventors:	Mark MURRAY and James KELLY

(7) A copy of the patent for which an extension is being sought, including the entire specification and claims, is attached as EXHIBIT 4.

(8) A receipt of maintenance fee payment has been issued with regard to U.S. Patent No. 4,845,075. A copy of the maintenance fee receipt is attached as EXHIBIT 5. No disclaimer, certificate of correction or reexamination certificate has been issued in connection with U.S. Patent No. 4,845,075.

(9) U.S. Patent No. 4,845,075, for which this extension is sought, generally claims proteins having two polypeptide chains, each of the chains comprising the amino acid sequence of the B-chain of PDGF and segments thereof, compositions comprising effective amounts of proteins derived from rhPDGF-BB, and methods for enhancing the wound healing process comprising administering such compositions. The active ingredient in the approved products, "Becaplermin Concentrate" and "REGRANEX®", is a recombinant form of human platelet-derived growth factor composed of two disulfide-linked B chain polypeptides (rhPDGF-BB). The approved product is indicated for the treatment of diabetic ulcers.

Claims 1-6:

1. An isolated protein having two polypeptide chains, each of said chains comprising the amino acid sequence of the B-chain of PDGF from amino acid 15 to amino acid 109.

2. An isolated protein having two polypeptide chains, each of said chains comprising the amino acid sequence of the B-chain of PDGF from amino acid 29 to amino acid 109.

3. An isolated protein having two polypeptide chains, each of said chains comprising the amino acid sequence of the B-chain of PDGF from amino acid 15 to amino acid 101.

4. An isolated protein having two polypeptide chains, each of said chains comprising the amino acid sequence of the B-chain of PDGF from amino acid 29 to amino acid 101.

5. An isolated protein having two polypeptide chains, each of said chains comprising the amino acid sequence of the B-chain of PDGF from amino acid 1 to amino acid 101.

6. An isolated protein having two polypeptide chains, each of said chains comprising the amino acid sequence of the B-chain of PDGF from amino acid 1 to amino acid 109.

* * * * *

The approved products are "Becaplermin Concentrate" and "REGRANEX®". The active ingredient in the approved products is a homodimer composed of two disulfide-linked B-chain polypeptides of PDGF. Claims 1-6 claim an isolated protein having two polypeptide chains, each of the chains comprising the amino acid sequence of the B-chain of PDGF and segments thereof. Thus, claims 1-6 read on the approved products, "Becaplermin Concentrate" and "REGRANEX®".

Claims 7-12:

7. An isolated protein having two polypeptide chains, each of said chains comprising the amino acid sequence of p28-sis corresponding to the B-chain of PDGF from amino acid 15 to amino acid 109.

8. An isolated protein having two polypeptide chains, each of said chains comprising the amino acid sequence of p28-sis corresponding to the B-chain of PDGF from amino acid 29 to amino acid 109.

9. An isolated protein having two polypeptide chains, each of said chains comprising the amino acid sequence of p28-sis corresponding to the B-chain of PDGF from amino acid 15 to amino acid 101.

10. An isolated protein having two polypeptide chains, each of said chains comprising the amino acid sequence of p28-sis corresponding to the B-chain of PDGF from amino acid 29 to amino acid 101.

11. An isolated protein having two polypeptide chains, each of said chains comprising the amino acid sequence of p28-sis corresponding to the B-chain of PDGF from amino acid 1 to amino acid 101.

12. An isolated protein having two polypeptide chains, each of said chains comprising the amino acid sequence of p28-sis corresponding to the B-chain of PDGF from amino acid 1 to amino acid 109.

* * * * *

The approved products are "Becaplermin Concentrate" and "REGRANEX®". The active ingredient in the approved products is a homodimer composed of two disulfide-linked B-chain polypeptides. Claims 7-12 claim an isolated protein having two polypeptide chains, each of the chains comprising the amino acid sequence of p28-sis corresponding to the B-chain of PDGF and segments thereof. p28-sis, derived from the v-sis gene, has a high degree of homology with the B-chain of PDGF differing at only four positions: 6, 7, 101 and 107. These amino acid differences are largely conservative and do not effect the biological activity of the B-chain. Thus, claims 7-12 read on the approved products.

Claim 13:

13. A wound-healing composition comprising a therapeutically effective amount of an isolated protein according to any one of claims 1-12, and a physiologically acceptable carrier or diluent.

* * * * *

The approved product "REGRANEX®" is a wound-healing composition. It contains a therapeutically effective amount of an isolated protein having two polypeptide chains, each of the chains comprising the amino acid sequence of the B-chain of PDGF and segments thereof. It is administered in an acceptable carrier or diluent as described in the insert (EXHIBIT 3). Thus, claim 13 reads on the approved product.

Claim 15:

15. The wound-healing composition of claim 13 including an adjuvant.

* * * * *

The approved product "REGRANEX®" includes an adjuvant, including for example, L-lysine which is a stabilizing substance. Thus, claim 13 reads on the approved product.

Claim 17:

17. A method for enhancing the wound healing process in a warm-blooded animal, comprising administering to the animal a composition according to any one of the claims 13-16.

* * * * *

The approved product "REGRANEX®" is a composition according to claim 13 and 15 to be administered to humans to promote the chemotactic recruitment and proliferation of cells involved in wound repair, specifically to increase the incidence of complete healing of diabetic ulcers, in accordance with the approved package insert (EXHIBIT 3). Thus, claim 17 reads on the approved product.

(10) The relevant dates and information pursuant to 35 U.S.C. § 156 (g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(a) Issue date of patent: July 4, 1989

(b) Effective Date of BB IND No. 3486 application: March 30, 1990

Date BB IND No. 3486 submitted: March 30, 1990

Date BB IND No. 3486 received by the FDA: March 30, 1990

(c) Date BLA No. 96-1408 (REGRANEX) submitted: Dec. 16, 1996

Date BLA No. 96-1422 (Becaplermin Concentrate) submitted: Dec. 16, 1996

Date BLA No. 96-1408 (REGRANEX) received: Dec. 16, 1996

Date BLA No. 96-1422 (Becaplermin Concentrate) received: Dec. 16, 1996

(d) Date BLA No. 96-1408 (REGRANEX) approved: Dec. 16, 1997

Date BLA No. 96-1422 (Becaplermin Concentrate) approved: Dec. 16, 1997

(11) A brief description of the significant activities undertaken by the marketing applicants, OMJ Pharmaceuticals, Inc., an affiliate of Ortho-McNeil Pharmaceutical Corporation, a wholly owned subsidiary of Johnson & Johnson, and Chiron Corporation, on behalf of the Applicant during the applicable regulatory review period with respect to the approved product, and the significant dates applicable to such activities, are set out in EXHIBIT 6.

(12) Applicant is of the opinion that U.S. Patent No. 4,845,075, is eligible for extension under 35 U.S.C. § 156 because it satisfies all the requirements for such an extension in as much as:

(i) the term of such patent has not expired before submission of this application (35 U.S.C. § 156(a)(1));

(ii) the term of such patent has never been extended (35 U.S.C. § 156(a)(2));

(iii) the application for extension is submitted by the owner of record, through undersigned counsel, in accordance with the requirements of 35 U.S.C. § 156(d);

(iv) the approved products, "Becaplermin Concentrate" and "REGRANEX®" have been subject to a regulatory review period before its commercial marketing or use (35 U.S.C. § 156(a)(4));

(v) the permission for the commercial marketing or use of the products, "Becaplermin Concentrate" and "REGRANEX®", after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of the Public Health Service Act under which such regulatory period occurred (35 U.S.C. § 156 (a)(5)(a)); and

(vi) no other patent has been extended for the same regulatory review period for the approved product (35 U.S.C. § 156(c)(4)).

Applicant requests an extension of the patent term of U.S. Patent No. 4,845,075 by 4.36 years (1593 days) from the original expiration date of July 4, 2006 to November 14, 2010. This period of extension is calculated according to the following subsections of 37 C.F.R. § 1.775:

(a) The original expiration date of the Patent is 17 years from the date of issue, that is July 4, 2006.

(c) The length of the regulatory review period was 2819 days, calculated as follows:

(1) The number of days from the effective date of original IND (BB) No. 3486 for the approved products, "REGRANEX®" and "Becaplermin Concentrate" to the receipt by the FDA of BLA No. 96-1408

(REGRANEX) and BLA No. 96-1422 (Becaplermin Concentrate), i.e., from March 30, 1990 to December 16, 1996 is 2453 days.

(2) The number of days between initial submission of the BLA No. 96-1408 (REGRANEX) and BLA No. 96-1422 (Becaplermin Concentrate) to the approval of the BLA's, that is from December 16, 1996 to December 16, 1997, is 366 days.

(d) The term of the patent as extended from a human drug product is to November 14, 2010, that is an extension of 1593 days, calculated by subtracting 1226 days from the 2819 days of the total regulatory review period from subparagraph (c):

(1) From the number of days of the regulatory review period calculated under subparagraph (c), the following are subtracted:

i) no part of the regulatory period was before the date on which the patent issued;

(ii) the number of days in the regulatory period as set forth in §1.775(c)(1) and §1.775(c)(1)(2) during which the marketing applicants on behalf of the Applicant, did not act with due diligence, which is zero (0) days; and

(iii) One-half the number of days remaining in the period as set forth in §1.775(c)(1) after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii), which is 1226 days (§ 1.775(c)(1) 2453 days ÷ 2 = 1226 days).

(2) Adding 1593 days to the original expiration date of July 4, 2006, comes to November 14, 2010.

(3) Adding 14 year to the date of approval of the BLA's comes to December 16, 2011.

(4) The earlier of the dates calculated under the subparagraphs (d)(2) and (3) above is November 14, 2010.

(5)(i) The original patent was issued after September 24, 1984. Adding 5 years to the original expiration date of the patent comes to July 4, 2011. The earlier of the dates calculated under the subparagraphs (d)(4) and (d)(5(i)) above is November 14, 2010.

(6) The original patent was not issued before September 24, 1984, so this paragraph is not applicable.

(13) Applicant, through its undersigned counsel, acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determinations to be made relative to the application for extension, in accordance with 37 C.F.R. § 1.765.

(14) A check in the amount of $1120, payable to the Commissioner of Patents and Trademarks is attached to cover the fee prescribed by 37 C.F.R. 1.20(j)(1) for receiving and acting upon this application for extension. If any additional fees are due, authorization is given to charge our deposit account number 03-1952.

(15) Please direct all inquiries and correspondence relating to this application for patent term extension to:

Gladys H. Monroy

Morrison & Foerster
755 Page Mill Road
Palo Alto, CA 94304
Phone: (650) 813-5711
Fax: (650) 494-0792

(16) Submitted herewith is a certification that these application papers are being submitted in duplicate (EXHIBIT 7).

(17) Additionally submitted herewith is a Declaration of Gladys H. Monroy as patent counsel for Applicant pursuant to 37 CFR § 1.740 (b)(1) as authorized by the Power of Attorney executed by Applicant submitted herewith as EXHIBIT 8.

Respectfully submitted,

By: Gladys H. Monroy
Gladys H. Monroy
Registration No. 32,430

Morrison & Foerster
755 Page Mill Road
Palo Alto, CA 94304-1018
Direct: (650) 813-5711
Fax: (650) 494-0792

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Note: this medical device has supplements. The device description may have changed. Be sure to look at the supplements to get an up-to-date view of this device.

Premarket Approval (PMA) Database

Trade Name	PERI-OSS
Classification Name	Bone Grafting Material, For Dental Bone Repair
Generic Name	Calcium Phosphate-Ceramic
Regulation Number	872.3930
Applicant	CURASAN AG
PMA Number	P800035
Date Received	06/12/1980
Decision Date	03/24/1981
Product Code	LPK
Notice Date	04/13/1981
Advisory Committee	Dental
Expedited Review Granted?	No

Supplements:

S001 S002 S003 S004 S005 S007 S008 S010 S011

Database Updated 11/07/2005

11

DEC 1 4 2000

K994337

510(k) Summary
Vitoss™ Scaffold Synthetic Cancellous Bone Void Filler

Submitted by	Address	Telephone	Contact Person
Orthovita, Inc.	45 Great Valley Parkway Malvern, PA 19355	(610) 640-1775	Angie Ide Director, Regulatory Affairs

	Subject Device	Predicate Device
Trade Name	*Vitoss*™ Scaffold Synthetic Cancellous Bone Void Filler	Pro Osteon 500$_R$ Resorbable Bone Void Filler
Common Name	Bone Void Filler	Bone Void Filler
Classification Name	Filler, Calcium Sulfate Preformed Pellets	Filler, Calcium Sulfate Preformed Pellets

Device Description:

Vitoss Scaffold is a porous calcium phosphate resorbable bone void filler for the repair of bony defects. It is an osteoconductive porous implant with a trabecular structure that resembles the multidirectional interconnected porosity of human cancellous bone. Pore diameters in the scaffold range from 1 μm to 1000 μm (1 mm). The implant is provided sterile in block and morsel forms.

Vitoss Scaffold guides the three-dimensional regeneration of bone in the defect site into which it is implanted. When *Vitoss* Scaffold is placed in direct contact with viable host bone, new bone grows in apposition to the calcium phosphate surfaces of the implant. As the implant resorbs, bone and other connective tissues grow into the space previously occupied by the scaffold. Results from animal studies demonstrate that eighty percent of *Vitoss* Scaffold is resorbed within twelve weeks.

Intended Use:

Vitoss Scaffold Synthetic Cancellous Bone Void Filler is intended only for use as a bone void filler for voids or gaps that are not intrinsic to the stability of the bony structure. *Vitoss* Scaffold is indicated for use in the treatment of surgically created osseous defects or osseous defects created from traumatic injury to the bone. *Vitoss* Scaffold should not be used to treat large defects that in the surgeon's opinion would fail to heal spontaneously.

Vitoss Scaffold is intended to be gently packed into bony voids or gaps of the skeletal system (i.e., the extremities, spine and pelvis). Following placement in the bony void

or gap, the calcium phosphate scaffold resorbs and is replaced with bone during the healing process.

Comparison to Predicate:

COMPARISON TO PREDICATE		
	Vitoss Scaffold	Pro Osteon 500R
Intended Use	Synthetic Bone Void Filler	Synthetic Bone Void Filler
Target Population	Individuals with bony defects resulting from surgery or trauma	Individuals with bony defects resulting from surgery or trauma
Anatomical Locations	Bony voids or gaps of the skeletal system, i.e., the extremities, spine and pelvis	Bony voids or gaps of the skeletal system, i.e., the extremities, spine and pelvis
Labeling	Labeling contains same intended use, contraindications, warnings, precautions, and adverse events as predicate	Labeling contains same intended use, contraindications, warnings, precautions, and adverse events as *Vitoss*
Materials		
• Chemical Composition	Calcium salt	Calcium salts
• Mineral Phase(s)	β-Tricalcium Phosphate $Ca_3(PO_4)_2$	Hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ Calcium Carbonate $CaCO_3$
Design		
• Physical Structure	Trabecular structure similar to cancellous bone	Trabecular structure similar to cancellous bone
• Porosity	Approximately 90%	Approximately 55%
• Pore Size (range)	1-1000μm	280-779μm
Performance		
• Osteoconductivity	Osteoconductive	Osteoconductive
• Resorption	Demonstrated as 76% resorbed at six weeks and 86% resorbed at twelve weeks	Reported as 20% resorbed at six weeks and 45% resorbed at twelve weeks
• Bone Remodeling Recorded as ratio of bone in implant to adjacent bone	Demonstrated as 0.6 at six weeks and 1.2 at twelve weeks	Demonstrated as 0.4 at six weeks and 0.5 at twelve weeks
• Mechanical Strength	Does not impart mechanical strength to surgical site	Does not impart mechanical strength to surgical site
Sterility	Sterilized by gamma radiation, single use only	Sterilized by gamma radiation, single use only
Biocompatibility	Established	Established
Dosage Form(s)	Morsels (1-4 mm sizes) and blocks (9x23mm cylinder)	Morsels (1-4 mm sizes)

Non-clinical Performance Data:

Pre-clinical animal data demonstrate that *Vitoss* Scaffold supports bone growth into a metaphyseal defect. These data show that *Vitoss* Scaffold resorbs at an early time period, accompanied by early bone ingrowth and bone remodeling. These results, in conjunction with biocompatibility data, demonstrate that *Vitoss* Scaffold Bone Void Filler is as safe and as effective as the predicate device, Pro Osteon 500R.

Clinical Performance Data:

Calcium-based ceramic materials, including tricalcium phosphate, have been used in clinical practice for more than 25 years with no remarkable safety issues. Early successful results were achieved in dentistry and oral reconstructive surgery. Subsequently, successful results have been demonstrated in the treatment of many orthopedic problems, including filling defects secondary to trauma, benign tumors and cysts, and the filling of metaphyseal defects of long bones.

In terms of safety, calcium-based bone void fillers have the advantage of avoiding the potential morbidity associated with the harvesting of bone autografts and the potential for disease transmission by allografts. To date there have been no reports in the literature of adverse reactions to calcium-based ceramic materials. A review of FDA's Manufacturer and User Facility Device Experience Database (MAUDE), conducted on 12/13/1999, showed no records of adverse device experience with Pro Osteon 500R, the device to which *Vitoss* Scaffold claims substantial equivalence. Only two records were found reported for all devices with the product code MQV. These two records were for Wright Medical's product, Osteoset, the device to which Pro Osteon 500R was determined to be substantially equivalent. This confirms the continued safe use of the bone void fillers currently in commercial distribution.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

DEC 1 4 2000

Ms. Angie Ide
Director, Regulatory Affairs
Orthovita Company
45 Great Valley Parkway
Malvern, Pennsylvania 19355

Re: K994337
Trade Name: Vitoss™ Scaffold Synthetic Cancellous Bone Void Filler
Regulatory Class: Unclassified
Product Code: MQV
Dated: October 26, 2000
Received: October 27, 2000

Dear Ms. Ide:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4659. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address "http://www.fda.gov/cdrh/dsma/dsmamain.html."

Sincerely yours,

for Mark N. Melkerson

Celia M. Witten, M.D., Ph.D.
Director
Division of General, Restorative, and
Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

INDICATIONS FOR USE STATEMENT

510(k) Number: K994337

Device Name: *Vitoss™ Scaffold* Synthetic Cancellous Bone Void Filler

Indications For Use:

Vitoss Scaffold Synthetic Cancellous Bone Void Filler is intended only for use as a bone void filler for voids or gaps that are not intrinsic to the stability of the bony structure. *Vitoss* Scaffold is indicated for use in the treatment of surgically created osseous defects or osseous defects created from traumatic injury to the bone. *Vitoss* Scaffold should not be used to treat large defects that in the surgeon's opinion would fail to heal spontaneously.

Vitoss Scaffold is intended to be gently packed into bony voids or gaps of the skeletal system (i.e., the extremities, spine and pelvis). Following placement in the bony void or gap, the calcium phosphate scaffold resorbs and is replaced with bone during the healing process.

PLEASE DO NOT WRITE BELOW THIS LINE
CONTINUE ON ANOTHER PAGE IF NEEDED

Concurrence of CDRH, Office of Device Evaluation (ODE)

(Division Sign-Off)
Division of General Restorative Devices
510(k) Number K994337

Prescription Use _____ OR **Over-The-Counter Use** _____
(Per 21 CFR 801.109)

510(k) Premarket Notification Database

Device Classification Name	Filler, Bone Void, Calcium Compound
510(K) Number	K032409
Regulation Number	888.3045
Device Name	VITOSS SCAFFOLD SYNTHETIC CANCELLOUS BONE VOID FI
Applicant	ORTHOVITA, INC. 45 Great Valley Pkwy. Malvern, PA 19355
Contact	Andreina Ide
Classification Product Code	MQV
Date Received	08/04/2003
Decision Date	08/29/2003
Decision	Substantially Equivalent (SE)
Classification Advisory Committee	Orthopedic
Review Advisory Committee	Physical Medicine
Statement/Summary/Purged Status	Summary Only
Summary	Summary
Type	Traditional
Reviewed By Third Party	No
Expedited Review	No

Database Updated 11/07/2005

AUG 2 9 2003

K032409

510(k) Summary
Vitoss® *Scaffold* Synthetic Cancellous Bone Void Filler

Submitted by	Address	Telephone	Contact Person
Orthovita, Inc.	45 Great Valley Parkway Malvern, PA 19355	(610) 640-1775	Andreina Ide, Sr. Director, Regulatory Affairs

	Subject Device	Predicate Devices
Trade Name →	*Vitoss*® Scaffold Synthetic Cancellous Bone Void Filler	▪ WMT-TCP K022629 ▪ chronOS K013072
Common Name	Resorbable Synthetic Bone Void Filler/Bone Graft Substitute	
Classification Name	Resorbable Calcium Salt Bone Void Filler Device	

Device Description:

Vitoss Scaffold is a porous calcium phosphate resorbable bone void filler for the repair of bony defects. It is an osteoconductive porous implant with a trabecular structure that resembles the multidirectional interconnected porosity of human cancellous bone. Pore diameters in the scaffold range from 1 μm to 1000 μm (1 mm). The implant is provided sterile in block and morsel forms.

Vitoss Scaffold guides the three-dimensional regeneration of bone in the defect site into which it is implanted. When *Vitoss* Scaffold is placed in direct contact with viable host bone, new bone grows in apposition to the calcium phosphate surfaces of the implant. As the implant resorbs, bone and other connective tissues grow into the space previously occupied by the scaffold. Results from animal studies demonstrate that eighty percent of *Vitoss* Scaffold is resorbed within twelve weeks.

Intended Use:

Vitoss Scaffold Synthetic Cancellous Bone Void Filler is intended for use as a bone void filler for voids or gaps that are not intrinsic to the stability of the bony structure. *Vitoss* Scaffold is indicated for use in the treatment of surgically created osseous defects or osseous defects created from traumatic injury to the bone. *Vitoss* Scaffold should not be used to treat large defects that in the surgeon's opinion would fail to heal spontaneously.

Vitoss Scaffold is intended to be packed into bony voids or gaps of the skeletal system (i.e., the extremities, spine and pelvis) and may be combined with autogenous blood

and/or bone marrow. Following placement in the bony void or gap, the calcium phosphate scaffold resorbs and is replaced with bone during the healing process.

Comparison to Predicate:

	Vitoss Scaffold	[illegible]	ChronOS
Intended Use	Resorbable Synthetic Bone Void Filler	Resorbable Synthetic Bone Void Filler	Resorbable Synthetic Bone Void Filler
Target Population	Individuals with bony defects resulting from surgery or trauma	Individuals with bony defects resulting from surgery or trauma	Individuals with bony defects resulting from surgery or trauma
Anatomical Locations	Bony voids or gaps of the skeletal system, i.e., the extremities, spine and pelvis	Bony voids or gaps of the skeletal system, i.e., the extremities, spine and pelvis	Bony voids or gaps of the skeletal system, i.e., the extremities, spine and pelvis
Labeling	Labeling contains same intended use as predicate devices	Labeling contains same intended use as *Vitoss Scaffold*	Labeling contains same intended use as *Vitoss Scaffold*
Materials	β-Tricalcium Phosphate $Ca_3(PO_4)_2$ satisfies ASTM F 1088	Tricalcium Phosphate – satisfies ASTM F 1088	β-Tricalcium Phosphate $Ca_3(PO_4)_2$ satisfies ASTM F 1088
Design			
• **Physical Structure**	Trabecular structure similar to cancellous bone	Trabecular structure similar to cancellous bone	Uniform, three-dimensional pore structure
• **Porosity**	Approximately 90%	Reported as "highly porous"	Approximately 60% to 70%
• **Pore Size (range)**	1-1000μm		100-500μm
Performance			
• **Osteoconductivity**	Osteoconductive	Osteoconductive	Osteoconductive
• **Resorption**	Demonstrated as 80% resorbed at twelve weeks	Reported as "resorbable"	Resorption reported to occur between 6 and 12 months.
• **Mechanical Strength**	Does not impart mechanical strength to surgical site	Does not impart mechanical strength to surgical site	Does not impart mechanical strength to surgical site
Sterility	Sterilized by gamma radiation, single use only	Sterilized by gamma radiation, single use only	Sterilized by gamma radiation, single use only
Biocompatibility	Established	Established	Established
Dosage Form(s)	Morsels and Blocks	Granules and Blocks	Granules, Cylinders and Blocks

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

AUG 2 9 2003

Ms. Andreina Ide
Sr. Director, Regulatory Affairs
Orthovita, Inc.
45 Great Valley Parkway
Malvern, PA 19355

Re: K032409
Trade Name: Vitoss Scaffold Synthetic Cancellous Bone Void Filler
Regulation Number: 21 CFR 888.3045
Regulation Name: Resorbable calcium salt bone void filler device
Regulatory Class: Class II
Product Code: MQV
Dated: August 1, 2003
Received: August 4, 2003

Dear Ms. Ide:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of Compliance at (301) 594-4659. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address http://www.fda.gov/cdrh/dsma/dsmamain.html

Sincerely yours,

for Mark N. Melkerson

Celia M. Witten, Ph.D., M.D.
Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

INDICATIONS FOR USE STATEMENT

510(k) Number: K032409

Device Name: *Vitoss® Scaffold* Synthetic Cancellous Bone Void Filler

Indications For Use:

Vitoss Scaffold Synthetic Cancellous Bone Void Filler is intended for use as a bone void filler for voids or gaps that are not intrinsic to the stability of the bony structure. *Vitoss* Scaffold is indicated for use in the treatment of surgically created osseous defects or osseous defects created from traumatic injury to the bone. *Vitoss* Scaffold should not be used to treat large defects that in the surgeon's opinion would fail to heal spontaneously.

Vitoss Scaffold is intended to be packed into bony voids or gaps of the skeletal system (i.e., the extremities, spine and pelvis) and may be combined with autogenous blood and/or bone marrow. Following placement in the bony void or gap, the calcium phosphate scaffold resorbs and is replaced with bone during the healing process.

PLEASE DO NOT WRITE BELOW THIS LINE
CONTINUE ON ANOTHER PAGE IF NEEDED

Concurrence of CDRH, Office of Device Evaluation (ODE)

for Mark N. Milhous

(Division Sign-Off)
Division of General, Restorative
and Neurological Devices

510(k) Number K032409

Prescription Use _____ OR **Over-The-Counter Use** _____
(Per 21 CFR 801.109)

12

PACKAGE INSERT

GEM 21S®
Growth-factor Enhanced Matrix

Caution: Federal Law restricts this device to sale by or on the order of a dentist or physician.

DEVICE DESCRIPTION:

GEM 21S® is a completely synthetic grafting system for bone and periodontal regeneration composed of a purified recombinant growth factor and a synthetic calcium phosphate matrix.

GEM 21S® is composed of two sterile components:

- synthetic beta-tricalcium phosphate (ß-TCP) [$Ca_3(PO_4)$] is a highly porous, resorbable osteoconductive scaffold or matrix that provides a framework for bone ingrowth, aids in preventing the collapse of the soft tissues and promotes stabilization of the blood clot. Pore diameters of the scaffold are specifically designed for bone ingrowth and range from 1 to 500 µm. The particle size ranges from 0.25 to 1.0 mm and

- highly purified, recombinant human platelet-derived growth factor-BB (rhPDGF-BB). PDGF is a native protein constituent of blood platelets. It is a tissue growth factor that is released at sites of injury during blood clotting. Extensive *in vitro* and animal studies have demonstrated its potent mitogenic (proliferative) and chemotactic (directed cell migration) effects on bone and periodontal ligament derived cells. Animal studies have shown PDGF to promote the regeneration of periodontal tissues including bone, cementum, and periodontal ligament (PDL).

The contents of the cup of ß-TCP are supplied sterile by gamma irradiation. Sterile rhPDGF-BB is aseptically processed and filled into the syringe in which it is supplied.

INDICATIONS:

GEM 21S® is indicated to treat the following periodontally related defects:

- Intrabony periodontal defects;
- Furcation periodontal defects; and
- Gingival recession associated with periodontal defects.

CONTRAINDICATIONS:

As with any periodontal procedure where bone grafting material is used, *GEM 21S®* is CONTRAINDICATED in the presence of one or more of the following clinical situations:

- Untreated acute infections at the surgical site;
- Untreated malignant neoplasm(s) at the surgical site;
- Patients with a known hypersensitivity to any product component (ß-TCP or rhPDGF-BB);
- Intraoperative soft tissue coverage is required for a given surgical procedure but such coverage is not possible; or
- Conditions in which general bone grafting is not advisable.

PACKAGE INSERT

GEM 21S®
Growth-factor Enhanced Matrix

WARNINGS:

The exterior of the cup and syringe are **NOT** sterile. See directions for use.
It is not known if *GEM 21S®* interacts with other medications. The use of *GEM 21S®* with other drugs has not been studied. Carcinogenesis and reproductive toxicity studies have not been conducted.

The safety and effectiveness of *GEM 21S®* has not been established:

- In other non-periodontal bony locations, including other tissues of the oral and craniofacial region such as bone graft sites, tooth extraction sites, bone cavities after cystectomy, and bone defects resulting from traumatic or pathological origin. GEM 21S® has also not been studied in situations where it would be augmenting autogenous bone and other bone grafting materials.
- In pregnant and nursing women. It is not known whether rhPDGF-BB is excreted in the milk of nursing women.
- In pediatric patients below the age of 18 years.
- In patients with teeth exhibiting mobility of greater than Grade II or a Class III furcation.
- In patients with frequent or excessive use of tobacco products.

Careful consideration should be given to alternative therapies prior to performing bone grafting in patients:

- Who have severe endocrine-induced bone diseases (*e.g.* hyperparathyroidism);
- Who are receiving immunosuppressive therapy; or
- Who have known conditions that may lead to bleeding complications (*e.g. hemophilia*).

The *GEM 21S®* grafting material is intended to be placed into periodontally related defects. It must not be injected systemically.

The radiopacity of *GEM 21S®* is comparable to that of bone and diminishes as *GEM 21S®* is resorbed. The radiopacity of *GEM 21S®* must be considered when evaluating radiographs as it may mask underlying pathological conditions.

PRECAUTIONS:

GEM 21S® is intended for use by clinicians familiar with periodontal surgical grafting techniques.
GEM 21S® is supplied in a single use kit. Any unopened unused material must be discarded and components of this system should not be used separately.

PACKAGE INSERT

GEM 21S®
Growth-factor Enhanced Matrix

HOW *GEM 21S®* IS SUPPLIED:

Each *GEM 21S®* kit consists of:

(1) one cup containing 0.5 cc of ß-TCP particles (0.25 to 1.0 mm); and

(2) one syringe containing a solution of 0.5 ml rhPDGF-BB (0.3 mg/ml).

All of these components/accessories are **for single use only**.

CLINICAL STUDY:

A 180 patient, double-blinded, controlled, prospective, randomized, parallel designed multicenter clinical trial in subjects who required surgical intervention to treat intraosseous periodontal defects was completed.

The major inclusion criteria were:

a. No localized aggressive periodontitis
b. Treatment site with the following characteristics:
   - Probing pocket depth ≥ 7mm at baseline,
   - After surgical debridement, ≥ 4mm vertical bone defect with at least 1 bony wall,
   - Sufficient keratinized tissue to allow complete tissue coverage of defect, and
   - Radiographic base of defect ≥ 3mm coronal to the apex of the tooth.

The major exclusion criteria were:

a. No periodontal surgery on the subject tooth within the last year.
b. No significant recent tobacco use.
c. Allergy to yeast-derived products.
d. Using an investigational therapy within the past 30 days.

The duration of the study was six (6) months following implantation of the product. Patients were randomized into three patient treatment groups:

- Group I (n=60): ß-TCP and 0.3 mg/ml rhPDGF-BB (*GEM 21S®*)
- Group II (n=61): ß-TCP and 1.0 mg/ml rhPDGF-BB
- Group III (n=59): ß-TCP and buffer alone (active control)

The baseline characteristics among the subjects in each group were similar with the exception of "base of defect to root apex". Group I had a mean defect which was significantly less than in Group III (6.5mm vs. 7.7mm, p=0.04).

Schedule of Patient Visits

Patients had 4 visits over the 6 months prior to surgery and device implantation. Scaling and root planing were performed if necessary within 3 months prior to the implant surgery date (Visit 5). Following implantation, subjects underwent 4 follow-up visits during the

first 24 days to assess wound healing and pain assessment and then 4 further follow-up visits every 6 weeks through 6 months. At these latter visits, clinical measurements and radiographs were performed.

Endpoints
The pre-defined primary effectiveness endpoint was the mean change in CAL between baseline and 6 months. Results were to be compared 1) for each group to a historically established level of effectiveness (mean change of 1.5 mm) and 2) between Group I and Group III. The pre-defined secondary endpoints included:

- Comparison of linear bone growth (LBG)
- Comparison of % bone defect fill (%BF) based on radiographs
- Area under the curve for change in CAL
- Change in CAL between baseline and 6 months
- Pocket depth reduction (PDR) change between baseline and 6 months
- Gingival recession (GR) change between baseline and 6 months
- Wound healing during first 3 weeks post-operatively

Primary Endpoint Results
The primary effectiveness endpoint was evaluated using the mean change in CAL gain (mm) from baseline to 6 months for each of the three groups. Mean changes at 6 months are presented in the Table below:

Group of Interest and Change	**Control Group and Change**	**Difference**	**p-value**
Group I 3.7 mm	Historical 1.5 mm	2.2 mm	***<0.001***
Group II 3.7 mm	Historical 1.5 mm	2.2 mm	***<0.001***
Group III 3.5 mm	Historical 1.5 mm	2.0 mm	***<0.001***
Group I 3.7 mm	Group III 3.5 mm	0.2 mm	0.20

As seen in the table above, all three groups, including the control group, had statistically and clinically meaningful mean CAL gains when compared to the historically established 1.5 mm level ($p<0.001$). At 6 months, there was no statistically or clinically significant difference in CAL gain for the low-concentration group (Group I) when compared to the active control without GEM 21S® ($p=0.20$). However, at 3 months (not included in the Table above), the difference was 0.5 mm (3.8 mm vs 3.3 mm) which was statistically significant ($p=0.04$) suggesting that the device may facilitate *earlier* resolution of periodontal intrabony lesions.

Secondary Endpoint Results

As noted above, numerous secondary endpoints were pre-defined in the clinical protocol. The results for these are presented in the Table below. The results represent changes from baseline to 6 months unless otherwise noted.

Parameter	Primary Group and Mean Change	Control Group and Mean Change	Difference in Means	p-value
Linear Bone Growth	Group I 2.52 mm	Group III 0.89 mm	1.63 mm	***<0.001***
	Group II 1.53 mm	Group III 0.89 mm	0.64 mm	***0.02***
% Bone Fill	Group I 56.0%	Group III 17.9%	38.1%	***<0.001***
	Group II 33.9%	Group III 17.9%	16.0%	***0.02***
AUC for CAL Gain (mm-weeks)	Group I 67.5	Group III 60.1	7.4	***0.05***
	Group II 61.8	Group III 60.1	1.7	0.35
CAL Gain	Group II 3.7 mm	Group III 3.5 mm	0.2 mm	0.29
PDR	Group I 4.4mm	Group III 4.2 mm	0.2 mm	0.38
	Group II 4.3 mm	Group III 4.2 mm	0.1 mm	0.66
PDR – 3 Months*	Group I 4.2 mm	Group III 4.2 mm	0.0 mm	0.80
	Group II 4.1 mm	Group III 4.2 mm	0.1 mm	0.67
GR	Group I 0.7 mm	Group III 0.7 mm	0.0 mm	0.95
	Group II 0.6 mm	Group III 0.7 mm	0.1 mm	0.81
GR – 3 Months*	Group I 0.5 mm	Group III 0.9 mm	0.4 mm	***0.04***
	Group II 0.7 mm	Group III 0.9 mm	0.2 mm	0.46

* Not a pre-defined secondary or primary endpoint.

The table illustrates that both the low- and high-dose device achieved significant improvement over the control device (no rhPDGF-BB) at 6 months for linear bone growth and percent bone fill. Although other parameters (CAL gain and gingival recession) showed significant changes at 3 months for the high-dose group, these benefits were not maintained

over control at 6 months. Again, several of these results suggest that the device facilitates *earlier* resolution of periodontal intrabony lesions.

Safety
There were 18 patients (7 Group I, 6 Group II, 5 Group III) with adverse events reported as related to the device. None of these were serious. They were all classified as surgical site reactions. There were no significant differences in the incidence of adverse events across the three treatment groups.

Conclusion
GEM 21S® was shown, by both clinical and radiographic measures, to be effective in treating moderate to severe periodontally related defects within six months of implantation. When implanted into bony defects of the periodontium, *GEM 21S®* has been shown to speed clinical attachment level (CAL) gain, reduce gingival recession, and improve bone growth resulting in increased bone fill of the osseous defect.

ADVERSE EVENTS:

Although no serious adverse reactions attributable to *GEM 21S®* were reported in a 180 patient clinical trial, patients being treated with *GEM 21S®* may experience any of the following adverse events that have been reported in the literature with regard to periodontal surgical grafting procedures: swelling; pain; bleeding; hematoma; dizziness; fainting; difficulty breathing, eating, or speaking; sinusitis; headaches; increased tooth mobility; superficial or deep wound infection; cellulitis; wound dehiscence; neuralgia and loss of sensation locally and peripherally; and, anaphylaxis.

Occurrence of one or more of these conditions may require an additional surgical procedure and may also require removal of the grafting material.

DIRECTIONS FOR USE:

ASEPTIC TECHNIQUE

- The contents of the cup of ß-TCP are supplied sterile by gamma radiation.
- Sterile rhPDGF-BB is aseptically processed and filled into the syringe in which it is supplied.

The exterior portion of the cup of ß-TCP and the exterior surface of the syringe are non-sterile. Because of this, it is recommended that transfer of the ß-TCP particles to a sterile container in the sterile operating field be performed in a sterile manner prior to adding the PDGF from the syringe. Care must also be taken to minimize crushing the ß-TCP particles. Appropriate sterile transfer techniques must be used to prevent contamination of the contents of the cup and syringe.

SURGICAL TECHNIQUE

Familiarization with the device and following proper surgical grafting techniques are extremely important when using *GEM 21S®*. Radiographic evaluation of the defect site

prior to use is essential to accurately assess the extent of the defect and to aid in the placement of the grafting material.

Following exposure of the defect with a full thickness mucoperiosteal flap, all granulation tissue must be carefully removed. Thorough soft tissue debridement of the defect is critical to successful regeneration. Granulation tissue, if left in the defect, could be stimulated by the rhPDGF-BB component, diminishing the desired regenerative response. Exposed tooth root surfaces should also be thoroughly planed.

Following thorough debridement of the osseous defect, the clinician, based on his or her experience, estimates the amount of *GEM 21S®* needed to fill the defect. For best results, *GEM 21S®* must completely fill the defect to the level of the surrounding bony walls. Overfilling should be avoided. The clinician prepares the *GEM 21S®* graft by fully saturating the ß-TCP particles with the rhPDGF-BB solution and letting the product sit for approximately ten (10) minutes. Proper aseptic technique must employed in preparing and applying *GEM 21S®*.

The saturated *GEM 21S®* should be placed into the defect using moderate pressure, taking care not to crush the particles. In order to enhance the formation of new bone, *GEM 21S®* should be placed in direct contact with well-vascularized bone. Excessive bleeding should be controlled prior to placing grafting materials. Following placement of the *GEM 21S®* and completion of any additional surgical steps, the mucoperiosteal flaps should be sutured to achieve primary closure wherever possible.

Postoperative patient management should follow the same regimen as similar cases utilizing autogenous bone grafting. Pre-requisites for all regenerative procedures include prevention of wound dehiscence, a stable clot and minimal bacterial contamination.

The *GEM 21S®* kit and its components must not be re-sterilized by any method or reused. Inspect each individual sterile component of the kit for structural integrity prior to use. If the seal of any inner or outer container is open, broken or otherwise damaged, the product must be assumed to be non-sterile and consequently, must not be used.

Any opened unused material must be discarded and components of this system should not be used separately.

STORAGE CONDITIONS:

The *GEM 21S®* kit must be refrigerated at 2°-8° C (36°-46° F). Do not freeze. The individual rhPDGF-BB component must be refrigerated at 2°-8° C (36°-46° F). The ß-TCP cup can be stored at room temperature, up to 30° C (86° F). The rhPDGF-BB component must be protected from light prior to use; do not remove from outer covering prior to use.

Do not use after the expiration date.

PACKAGE INSERT

GEM 21S®
Growth-factor Enhanced Matrix

BIOCOMPATIBILITY:

GEM 21S® biocompatibility has been demonstrated in accordance with the International Standard ISO 10993-1:1997 "Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing."

Manufactured By:

BioMimetic Therapeutics, Inc.
389-A Nichol Mill Lane
Franklin, TN 37067

Distributed By:

Osteohealth Company
Division of Luitpold Pharmaceuticals, Inc.
One Luitpold Drive
PO Box 9001
Shirley, NY 11967
(800) 874-2334

This product is sold and distributed under US patents:
4,845,075
5,045,633
5,124,316

November 18, 2005

KLEER-FAX RECYCLED

80000 SERIES
10% P.C.W.

BIOMIMETIC GEM 21 S PRODUCT - FDA CHRONOLOGY

Date	***Activity***
13-Dec-01	BMTI original submission of IDE submission
11-Jan-02	Original IDE submission deficiencies identified by FDA
15-Jan-02	BMTI responded to FDA's January 6, 2003 telephone inquiry for additional information on Interim Analysis
31-Jan-02	BMTI response to FDA's January 11, 2002 deficiencies
28-Feb-02	FDA conditionally approved IDE
18-Mar-02	BMTI response to FDA's February 28, 2002 conditional approval revising the pivotal study protocol to include an interim analysis
24-Apr-02	FDA approves BMTI's response to FDA's February 28, 2002 conditional approval
17-Jul-02	Notification of the IRB approval
24-Sep-02	BMTI submits Interim Analysis Protocol (statistical plan)
26-Sep-02	FDA does not approve revisions to the Statistical Analysis Plan
10-Oct-02	FDA approves (via phone) Interim Analysis Protocol (statistical plan)
03-Dec-02	BMTI submitted results of the November 18, 2002 interim statistical analysis
Week of 6-Jan-03	FDA requested (via phone) additional details regarding interim statistical analysis
17-Feb-03	FDA approves (via phone) BMTI response to FDA's January 6, 2003 telephone inquiry for additional information on Interim Analysis
05-May-03	BMTI submitted a revision copy of the statistical analysis plan to change concentration of PDGF to 0.3mg/ml
09-May-03	FDA approves revision copy of the statistical analysis plan to change concentration of PDGF to 0.3mg/ml
29-Jul-03	BMTI submitted annual report in accordance with 21 CRF 812.150(b)(5)
25-Aug-03	FDA approves (via phone) annual report submitted in accordance with 21 CRF 812.150(b)(5)
27-Aug-03	BMTI submitted a revision to the Statistical Analysis Plan
11-Sep-03	BMTI submitted changes to August 27, 2003 Statistical Analysis Plan
24-Oct-03	BMTI submitted response to FDA's September 26 explanation of deficiencies regarding revisions to the Statistical Analysis Plan
25-Nov-03	FDA approves revisions to Statistical Analysis Plan
24-Dec-03	BMTI submitted Pre-PMA filing meeting and a draft of the Clinical Study Report.
29-Dec-03	FDA requested additional details (via telephone call) regarding submitted Pre-PMA filing meeting and draft of the Clinical Study Report
28-Jan-04	FDA approved Pre-PMA filing meeting and a draft of the Clinical Study Report.
28-Jan-04	FDA acknowledges and closes completion of IDE
09-Feb-04	Minutes of February 3, 2003 Pre-PMA filing review
09-Feb-04	BMTI submits Pre-PMA Meeting Minutes

Date	Activity
10-Feb-04	FDA receipt of Pre-PMA Meeting Minutes
12-Mar-04	PMA Submission Original Acknowledgement Receipt
24-Mar-04	PMA Revision; Typographical Errors
25-Mar-04	FDA receives PMA Revision
09-Apr-04	Transmittal Letter, Updated SS&E w/ PDF
14-Apr-04	CBER Response to PDGF RE: Purity, Potency, and Consistency of PDGF
16-Apr-04	FDA accepts PMA for filing
26-Apr-04	FDA schedules dental products panel of the Medical Devices Advisory Committee Meeting for July 13, 2004
19-May-04	FD 482 Notice for BIMO Audit at BMTI
02-Jun-04	Teleconference call minutes; additional information on b-TCP
03-Jun-04	BMTI submits Table of Contents 5 Volume Non-Public Release Sponsors' Panel Package
04-Jun-04	BMTI submits Table of Contents 2 Volume Public Panel Package
04-Jun-04	FDA receives Table of Contents 5 Volume Non-Public Release Sponsors' Panel Package
05-Jun-04	FDA receives Table of Contents 2 Volume Public Panel Package
23-Jun-04	FDA 483 from Kristin S. Tharp of the FDA to Dr. Thomas Hahn, DDS.
29-Jun-04	BMTI responded on behalf of Dr. Hahn to FDA 483 from KS Tharp.
02-Jul-04	BMTI updated letter of cross-reference to Orthovita
02-Jul-04	BMTI submitted response to FDA request for supplementary Statistical Analyses
07-Jul-04	FDA received updated letter of cross-reference to Orthovita
07-Jul-04	FDA received BMTI rsponse to FDA request for supplementary Statistical Analyses
08-Jul-04	BMTI submitted Manufacturing Validation Reports
16-Jul-04	MAF-1294 Orthovita; Notification of cross-reference
23-Jul-04	Transmittal of Panel Information
26-Jul-04	IDE vs. Commercial Manufacturing
27-Jul-04	BMTI submitted Bioassay Report in reference to amendment A005
27-Jul-04	BMTI submitted Kendall Healthcare Reference Information via Fax
28-Jul-04	FDA received Bioassay Report in reference to amendment A005
30-Jul-04	BMTI emailed FDA responding to telephone inquiry on comparison's between IDE stage and PMA stage
03-Aug-04	BMTI submitted to FDA amendment comparing PDGF component clinical vs. commercial to show that there was not change from the IDE submission to the PMA
04-Aug-04	FDA acknowledge receipt of BMTI August 3, 2004 amendment
05-Aug-04	BMTI submitted reference to A006, electronic copy (PDF) of PMA Amendment to Dr. Stromberg
05-Aug-04	BMTI submitted reference to A006, electronic copy (PDF) of PMA Amendment to Angela Blackwell

Date	Activity
12-Aug-04	Compliance Deficiency Letter on Cannula; Insufficient Information regarding Amendment A005
25-Aug-04	BMTI submitted amendment to FDA addressing question the FDA had on Kendall Healthcare cannula being used in GEM 21S kit
31-Aug-04	BMTI submitted to FDA and amendment comparing β-TCP IDE vs. PMA (Clinical vs. Commercial)
03-Sep-04	FDA acknowledge receipt of BMTI August 31, 2004 amendment
09-Sep-04	The Agency Acknowledged response in a September 9, 2004 letter to Dr. Hahn
14-Sep-04	FDA acknowledge receipt of BMTI August 25, 2004 amendment
21-Sep-04	BMTI's Letter of Reference to Osteohealth for IDE
22-Sep-04	FDA receives BMTI's Letter of Reference to Osteohealth for IDE
29-Sep-04	Deficiency Letter from the FDA on Amendments A001-A009
06-Oct-04	BMTI acknowledgement of September 29, 2004 Letter from FDA
07-Oct-04	FDA receives BMTI acknowledgement of September 29, 2004 Letter
08-Oct-04	BMTI submits Label, Insert, & SS&E
12-Oct-04	BMTI submits electronic version of SS&E, Label
12-Oct-04	FDA receives Label, Insert, & SS&E
13-Oct-04	FDA receives electronic version of SS&E, Label
22-Oct-04	BMTI response to September 29, 2004 Letter (Analytical Method Validation Report - GEM 21S™ Bioassay Validation Summary)
27-Oct-04	BMTI response to September 29, 2004 Letter (Analytical Report - Validation of Biochemical Analytical Techniques used for the Characterization of rhPDGF-BB)
28-Oct-04	FDA receives BMTI response to September 29, 2004 Letter (Analytical Method Validation Report - GEM 21S™ Bioassay Validation Summary)
28-Oct-04	FDA receives BMTI response to September 29, 2004 Letter (Analytical Report - Validation of Biochemical Analytical Techniques used for the Characterization of rhPDGF-BB)
01-Nov-04	BMTI response to September 29, 2004 Letter (Validation Summary Report - Validation Summary Report for the Sterility Validation for the B-TCP 0.5cc Small Perio Cup)
03-Nov-04	FDA receives BMTI response to September 29, 2004 Letter (Validation Summary Report - Validation Summary Report for the Sterility Validation for the B-TCP 0.5cc Small Perio Cup)
05-Nov-04	Electronic PDF copy of PMA Amendments A016 & A017 to Dr. Stromberg
05-Nov-04	E-mail correspondence with Keisha Thomas and Vertleen Covington to schedule a compliance audit for PMA 040013.
05-Nov-04	E-mail correspondence with Angela Blackwell showing time frames of Amendment submissions 15, 16 & 17
10-Nov-04	E-mail correspondence with Angela Blackwell; attached a revised copy of the SS&E and Package Insert per her request

Date	Activity
24-Dec-04	Follow-up to December 13, 2004 conference call.
27-Jan-05	Fax response from Angela Blackwell to BMTI's October 28, 2004 response to major deficiencies indicating inadequacies.
01-Feb-05	BMTI response to January 27, 2005 Agency Telephone Inquiry [Supplementary Manufacturing Information on Packaging Validation (Shipping & Distribution)]
02-Feb-05	E-mail correspondence with Thinh Nguyen of the FDA; attached a copy of the August 2004 Kendall Healthcare Reference Information
03-Feb-05	BMTI submits response to January 27, 2005 Agency Telephone Inquiry (Audit Contacts)
03-Feb-05	BMTI response to January 27, 2005 Agency Telephone Inquiry [Supplementary Manufacturing Information on Sterility Validation for GEM 21S™ rhPDGF-BB]
03-Feb-05	FDA receives BMTI response to January 27, 2005 Agency Telephone Inquiry [Supplementary Manufacturing Information on Packaging Validation (Shipping & Distribution)]
04-Feb-05	Dr. Stromberg requesting RP-HPLC assay data via e-mail on stability and transport validation. Dr. Hart responded indicating near completion on this information.
04-Feb-05	FDA receives BMTI response to January 27, 2005 Agency Telephone Inquiry (Audit Contacts)
04-Feb-05	FDA receives BMTI response to January 27, 2005 Agency Telephone Inquiry [Supplementary Manufacturing Information on Sterility Validation for GEM 21S™ rhPDGF-BB]
09-Feb-05	BMTI submits electronic PDF copy of PMA Amendments A018, A019 & A020 to Angela Blackwell
11-Feb-05	BMTI submits response to February 11, 2005 telephone Inquiry (Cannula Sterilization and shipping Information)
11-Feb-05	BMTI submits electronic PDF copy of PMA Amendment A022 to Angela Blackwell
14-Feb-05	FDA receives response to February 11, 2005 telephone Inquiry (Cannula Sterilization and shipping Information)
15-Feb-05	BMTI submits response to February 15, 2005 Agency E-mail (Kurt Stromberg) [Missing page from PMA Amendment A020 (Shipping of rhPDGF-BB Filled Syringes manufacturing report)]
15-Feb-05	BMTI submits response to February 15, 2005 Agency E-mail (Kurt Stromberg) [Shipment of Product SOP (ref. MFP003)]
15-Feb-05	Dr. Hart e-mailed Dr. Stromberg a copy of the validation report in response to question No. 9 of the January 27, 2005 letter
15-Feb-05	E-mail Correspondence from Kurt Stromberg requesting Shipping Request SOP (MFP003) and missing page from PMA Amendment A020

Date	Activity
16-Feb-05	Dr. Hart e-mailed Dr. Stromberg a copy of Bioassay Transfer Summary (att. 7) in response to question No. 1 of the January 27, 2005 letter.
16-Feb-05	BMTI submits Electronic PDF copy of PMA Amendment A022 & A023 to Angela Blackwell
16-Feb-05	BMTI submits electronic PDF copy of PMA Amendment A023 & A024 to Dr. Kurt Stromberg
16-Feb-05	FDA receives BMTI's response to February 15, 2005 Agency E-mail (Kurt Stromberg) [Missing page from PMA Amendment A020 (Shipping of rhPDGF-BB Filled Syringes manufacturing report)]
16-Feb-05	FDA receives BMTI's response to February 15, 2005 Agency E-mail (Kurt Stromberg) [Shipment of Product SOP (ref. MFP003)]
28-Feb-05	BMTI submits E-mail response to Dr. Kurt Stromberg regarding comments made by Agency on January 27, 2005 fax to BMTI (refer to Appendix 40 above)
01-Mar-05	BMTI submits Canine Study Audit Report submitted to Linda Sacco of NY District Division
01-Mar-05	BMTI submits Response to FDA inquiry on traceability of rhPDGF-BB conformance lots
02-Mar-05	BMTI submits response to FDA inquiry on SDS-PAGE; rhPDGF-BB conformance lots
02-Mar-05	BMTI sends correspondence to Susan Runner of the FDA on the March 1, 2005 Canine Study Audit Report that was submitted to Linda Sacco (refer to Appendix 54)
02-Mar-05	FDA receives BMTI's response to FDA inquiry on traceability of rhPDGF-BB conformance lots
02-Mar-05	Faxed agenda from Angela Blackwell for the March 3, 2005 Teleconference regarding timetables from January 27, 2005 fax (see Exhibit 40), etc.
03-Mar-05	FDA requested an electronic copy of the July 8, 2004 PMA submission
03-Mar-05	Electronic PDF copy of sections 6.21.1.15.34 – 6.21.1.15.38 and Attachment 6.21.15.7.21 of PMA Amendment A005 to Angela Blackwell
03-Mar-05	March 3, 2005 Draft minutes of telephone conference between BMTI and FDA on timetables, sterilization issues, packaging issues.
03-Mar-05	FDA receives BMTI response to FDA inquiry on SDS-PAGE; rhPDGF-BB conformance lots
04-Mar-05	BMTI provided additional information regarding stability data
04-Mar-05	Electronic PDF copy of PMA Amendment A024 to Angela Blackwell
04-Mar-05	Electronic PDF copy of PMA Amendment A024 to Dr. Kurt Stromberg
04-Mar-05	Notification to the Mary Jo Robinson of the Agency that Amendment A018 was assigned twice and needed correction.
04-Mar-05	Tyco responding directly to the agency with the Kendall Blunt Needle resubmission

Date	Activity
04-Mar-05	FDA acknowledged receipt of electronic copy of July 8, 2004 submission regarding stability data and requested additional information regarding stability data
05-Mar-05	FDA left voice message requesting information on rpHPLC validation
07-Mar-05	BMTI provided additional information regarding stability data
07-Mar-05	BMTI submits Response to FDA's inquiry on Canine Study. Originally submitted to Linda Sacco on March 1, 2005
07-Mar-05	FDA requested that stability data be submitted as one complete package
08-Mar-05	FDA receives BMTI March 7 response to FDA's inquiry on Canine Study.
08-Mar-05	Dr. Stromberg requesting, via e-mail, a 14 item response from BMTI regarding the January 26, 2005 letter
09-Mar-05	Dr. Hart responding, via e-mail, to the Dr. Strombergs voice-mail requesting information on rpHPLC validation.
09-Mar-05	Angela Blackwell responded (via telephone acknowledging that Amendment A018 was assigned twice and needed correction.
09-Mar-05	BMTI respondedg, via e-mail, to FDA voice-mail requesting information on rpHPLC validation.
11-Mar-05	BMTI follow-up to the March 5, 2005 telephone call to include an attachment of the handling of rhPDGF-BB.
14-Mar-05	Patheon directly submitted information to the Agency on Autoclave Sterilization Validation for rhPDGF-BB Component
15-Mar-05	BMTI telephone call with Dr. Stromberg on Arg32 levels and rationale for 24 month expiry date
17-Mar-05	Dr. Hart follow-up to the February e-mail sent to Dr. Stromberg per his request. Dr. Hart included the e-mail along with the bioassay data table for stability samples.
17-Mar-05	Angela Blackwell requesting additional info on the Cannula.
18-Mar-05	BMTI reply to Angela Blackwell request for additional info on the Cannula.
18-Mar-05	Mark Citron e-mailed A. Blackwell a draft copy of the GEM 21S Package Performance Test; supplementary Sterility Test
18-Mar-05	FDA receives Patheon information on Autoclave Sterilization Validation for rhPDGF-BB Component
21-Mar-05	FDA requested summarization of BMTI's changes in response to February 28, 2005 correspondence to FDA
21-Mar-05	BMTI sent e-mail to Thinh Nguyen of FDA to acknowledge Sterilization Validation information for the autoclaves at Patheon requested by Bob Riley will be part of PMA filing
21-Mar-05	BMTI responded to FDA request for summarization of BMTI's changes in response to February 28, 2005 correspondence to FDA

Date	Activity
22-Mar-05	BMTI notified Dr. Stromberg, via e-mail, of the proposed latest changes to the response letter to the January 27, and February 15, 2005 agency e-mails relating to SDS page and bioassay issue.
22-Mar-05	BMTI follow-up, via e-mail, with Angela Blackwell regarding verification of amendment numbers
23-Mar-05	Correspondence from BMTI to FDA regarding SDS page and bioassay issue.
24-Mar-05	Tyco responding directly to the agency with additional Kendall Blunt Needle information
24-Mar-05	BMTI e-mailed Dr. Stromberg as a follow-up to the March 23, 2005 telephone call. Jim provided Dr. Stromberg a table outlining historical correspondence between BMTI and the Agency
24-Mar-05	BMTI submits response to FDA inquires from January 27, 2005 e-mail and other correspondence
25-Mar-05	FDA receives Tyco responds to the agency regarding additional Kendall Blunt Needle information
28-Mar-05	Jim Monsor e-mailed Joan Loreng of FDA on Audit schedule in UK. Amendment 31
30-Mar-05	Correspondence from FDA to BMTI regarding SDS page and bioassay issue.
30-Mar-05	Correspondence from FDA to BMTI regarding SDS page and bioassay issue.
30-Mar-05	Joan Loreng of FDA requested volumes 4 & 5 of Amendment 31
01-Apr-05	BMTI submits package insert correction from March 24, 2005 submission (see A030). Also submitted revised kit labeling showing that the cannula was removed
04-Apr-05	Electronic PDF copy of PMA Amendment A030 sent to Joan Loreng of FDA.
04-Apr-05	Electronic PDF copy of PMA Amendment A031 sent to A. Blackwell of FDA.
04-Apr-05	FDA receives package insert correction from March 24, 2005 submission (see A030) and revised kit labeling showing that the cannula was removed
07-Apr-05	Electronic PDF copy of PMA Amendment A005 (Volumes 5(a),(b),(c) and 6(a),(b) sent to Joan Loreng of FDA.
07-Apr-05	E-mail to Joan Loreng from Jim Monsor to confirm receipt of information requested for UK audits.
07-Apr-05	BMTI PMA follow-up commitments to Kurt Stromberg via e-mail from Jim Monsor.
11-Apr-05	Confirmation of audit dates for FDA inspection at BMTI facility and driving directions
13-Apr-05	BMTI submits Supplementary Stability Information (Use of Reverse Phase HPLC Method as a Stability Indicating Assay)

Date	Activity
13-Apr-05	FDA internal correspondence on PMA review for GEM 21S. Received from Cherie Parker.
14-Apr-05	BMTI submits electronic PDF copy of PMA Amendment A032 sent to Dr. Kurt Stromberg of FDA.
14-Apr-05	BMTI submits electronic PDF copy of PMA Amendment A032 sent to A. Blackwell of FDA.
14-Apr-05	BMTI submits electronic copy of requested QSIT audit documentation from April 13, 2005 FDA Audit.
14-Apr-05	FDA receives Supplementary Stability Information (Use of Reverse Phase HPLC Method as a Stability Indicating Assay)
19-Apr-05	Kurt Stromberg (FDA) inquired of stability and photostability information.
20-Apr-05	Charlie Hart responded to Kurt Stromberg (FDA) inquiry of stability and photostability information.
20-Apr-05	Response letter from FDA to Dr. Robert Genco regarding Feb 22-Mar 4, 2005 audit of University of NY at Buffalo facility
21-Apr-05	BMTI response to April 21, 2005 request from Cherie Parker re: the QSIT audit. Submitted additional information on Amendment 031
21-Apr-05	BMTI response to April 18, 2005 request from Cherie Parker re: QSIT audit. Submitted summary information on rhPDGF-BB sterile fill validations at Patheon.
22-Apr-05	BMTI supplier responded to Form FDA 483 from Joan Loreng of the FDA.
22-Apr-05	Form FDA 483 from Joan A. Loreng of the FDA sent to BMTI supplier.
22-Apr-05	Tyco submitted correct Validation Report on the Kendall Blunt Needle to the Agency
26-Apr-05	FDA receives Tyco correct Validation Report on the Kendall Blunt Needle to the Agency
28-Apr-05	Form FDA 483 from Joan A. Loreng of the FDA to BMTI supplier.
01-May-05	Letter from FDA summarizing inspection results from the February 22 through March 4, 2005 audit of SUNY at Buffalo
04-May-05	Howard Holstein of Hogan & Hartson e-mailed Thinh Nguyen of the FDA to discuss status of PMA
06-May-05	M. Citron e-mailed Thinh Nguyen of the FDA as a follow-up to their May 6, 2005 telephone conversation on additional rhPDGF-BB studies from BMTI supplier
06-May-05	FDA contact report on Inquiry of PMA A033 from Tom Golden
10-May-05	Kurt Stromberg of the FDA e-mailed Jim Monsor and Charlie Hart inquiring when bioassay and SDS-Page would be submitted to CDER
11-May-05	BMTI responded FDA's inquiry regarding when bioassay and SDS-Page would be submitted to CDER.
13-May-05	Charlie Hart e-mailed Kurt Stromberg of the FDA on follow-up to Kurt's May 10, 2005 e-mail regarding the Bioassay.

Date	Activity
13-May-05	M. Citron e-mailed Thinh Nguyen of the FDA to see if he had spoken with Dr. Runner.
13-May-05	FDA replied to BMTI May 13 email.
17-May-05	BMTI submitted Supplementary Information on rhPDGF-BB Component
17-May-05	Kurt Stromberg e-mailed Charlie Hart inquiring on Photostability Study.
17-May-05	Electronic PDF copy of PMA Amendment A034 sent to Dr. Kurt Stromberg of FDA.
18-May-05	Electronic PDF copy of PMA Amendment A034 sent to A. Blackwell of FDA.
18-May-05	FDA received Supplementary Information of rhPDGF-BB Component
18-May-05	BMTI responded to FDA's inquiry regarding Photostability Study.
19-May-05	Mark Citron e-mailed Thinh Nguyen of the FDA regarding concerns on additional bioassay testing that was requested by Kurt Stromberg
19-May-05	Kurt Stromberg of the FDA e-mailed Mark Citron regarding explanation of bioassay request.
19-May-05	BMTI responded to FDA e-mail of May 19 indicating its main objective on moving forward without further testing.
25-May-05	C. Hart e-mailed Kurt Stromberg on Bioassay data information along with a Draft copy of Statistical Analysis of rhPDGF-BB Mitogenic Bioassay data.
31-May-05	BMTI submitted letter to FDA FOI for copy request of EIR for the State University of New York at Buffalo Audit (2/22-3/4 2005)
31-May-05	BMTI submitted letter to FDA FOI for copy request of EIR for BioMimetic Pharmaceuticals Audits (5/19/04 & 4/13/05)
31-May-05	BMTI submitted letter to FDA FOI for copy request of EIR for Thomas Han Audit (6/9-10, 15, 22-23 2005)
02-Jun-05	FDA acknowledge receipt of BMTI letter to FDA FOI for copy request of EIR for BioMimetic Pharmaceuticals Audits (5/19/04 & 4/13/05)
03-Jun-05	M. Citron confirming June 20th Bioassay conference calls with the FDA. Also verifying that all other issues have been addressed.
06-Jun-05	Charlie Hart e-mailed Judy Chen of the FDA the revised protocol on the GEM 21S bioassay to review
09-Jun-05	C. Hart requesting from Dr. Stromberg of FDA Biostatistician feedback.
09-Jun-05	FDA acknowledge receipt of BMTI letter to FDA FOI for copy request of EIR for the State University of New York at Buffalo Audit (2/22-3/4 2005)
15-Jun-05	M. Citron e-mailed Angela Blackwell inquiring on info for June 22, 2005 teleconference
16-Jun-05	FDA acknowledge receipt of BMTI letter to FDA FOI for copy request of EIR for Thomas Han Audit (6/9-10, 15, 22-23 2005)
22-Jun-05	Status telephone conference with FDA to resolve GEM 21S approval open issues

Date	Activity
24-Jun-05	BMTI emailed FDA acknowledging June 22, 2005 teleconference on progress of GEM 21S Approval.
28-Jun-05	E-mail to Dr. Stromberg of FDA with draft bioassay protocol and report to progress approval for GEM 21S
29-Jun-05	FDA replied to BMTI June 24 email, and requested a copy of GEM 21S labeling
30-Jun-05	Dr. Stromberg of FDA replying to Meeting Minutes from June 22, 2005 teleconference call with additions and changes
30-Jun-05	BMTI responded to FDA June 29 request and provided GEM 21S labeling
06-Jul-05	BMTI e-mailed FDA to address remaining issues to satisfy the Agencies requirements for GEM 21S approval. K. Stromberg responded requesting shipping validation info
12-Jul-05	Mark Citron e-mailed Angela Blackwell and Mary Runner of the FDA on the supplementary information requested by CDER.
12-Jul-05	A. Blackwell requested a word version of the SS&E and Package Insert.
12-Jul-05	A. Blackwell notified M. Citron to inform DMC of BMTI's address change.
13-Jul-05	M. Citron notified A. Blackwell that bioassay statistics came out fine
13-Jul-05	BMTI submitted 18 Month Stability report; rhPDGF-BB Component Amendment
14-Jul-05	BMTI submitted rhPDGF-BB Component; Mitogenic Bioassay Supplementary Data Amendment
14-Jul-05	BMTI Notified PMA Document Mail Center of new address
14-Jul-05	C. Hart faxed K. Stromberg raw data of the BMTI bioassay data
14-Jul-05	FDA received 18 Month Stability report; rhPDGF-BB Component Amendment
15-Jul-05	Electronic PDF copy of PMA Amendment A035 & A036 sent to Dr. Kurt Stromberg of FDA.
15-Jul-05	Electronic PDF copy of PMA Amendment A035 & A036 sent to A. Blackwell of FDA.
15-Jul-05	BMTI submitted study report regarding bioassay to FDA
16-Jul-05	M. Citron (BMTI) followed-up, via e-mail, with Thinh Nguyen of the FDA to relay results of bioassay and to request quick turn-around for GEM 21S approval.
26-Jul-05	BMTI submits Inspection Responses to the FDA from the May 16-20, 2005 audit of BMTI supplier
27-Jul-05	FDA responded to BMTI July 6 email, and requested shipping validation information
28-Jul-05	BMTI submitted to FDA the shipping validation information requested on July 27, 2005
28-Jul-05	Howard Holstein e-mailed M. Kramer and L. Weinstein of the FDA to follow-up from previous discussions and clarify PMA Approval problems

Date	Activity
29-Jul-05	Angela Blackwell emailed BMTI with FDA's edited version of the GEM 21S Package insert.
29-Jul-05	BMTI forwarded Angela Blackwell July 29 emailed to Thin Nguyen
02-Aug-05	BMTI responded to FDA August 2 request, and acknowledged that amendment would take place
02-Aug-05	FDA replied study report submitted on July 15, 2002, and requested to amend an AAI Bioassay.
03-Aug-05	BMTI e-mailed Dr. Runner of FDA as a follow-up to August 2, 2005 conference call. This e-mail was forwarded to Thinh Nguyen as well.
03-Aug-05	BMTI e-mailed Patricia Love of the FDA notifying her of productive 8/2/05 conference with the agency
05-Aug-05	BMTI letter to Dr. Runner of the FDA addressing concerns with FDA's decisions from 8/4/05 teleconference call
08-Aug-05	BMTI submits Bioassay; Method Revision
08-Aug-05	BMTI submits electronic PDF copy of PMA Amendment A038 sent to Dr. Kurt Stromberg of FDA.
08-Aug-05	BMTI submits electronic PDF copy of PMA Amendment A038 sent to A. Blackwell of FDA.
09-Aug-05	BMTI e-mailed Dr. Runner of the FDA thanking her for looking into the issues surrounding the issues that are holding up approval
09-Aug-05	BMTI e-mailed Dr. Stromberg of the FDA regarding the Stability Specification clarification
16-Aug-05	BMTI e-mailed Dr. Runner of the FDA with information on Commercial Inventory for GEM 21S and notifying her that BMTI supplier is available to assist the Agency
17-Aug-05	BMTI sent letter notifying Dr. Susan Runner of CDRH of recent teleconference call with Dr. Love of the Combination Products Division. The letter also granted FDA permission to speak with BMTI supplier on PMA matters related to BioMimetic's GEM 21S
18-Aug-05	BMTI e-mailed Angela Blackwell of the FDA asking her to contact him if she has questions regarding units used in the bioassay
18-Aug-05	BMTI notified Dr. Patricia Love via e-mail that BMTI supplier is waiting to hear from the FDA on potential questions regarding their manufacturing facility.
19-Aug-05	BMTI provided Dr. Stromberg Draft of study procedure on Bioassay results
23-Aug-05	Communication with the FDA regarding request for four recent PMA amendment titles from PMA Center
23-Aug-05	BMTI emailed FDA expressing concerns regarding FDA's request for additional protocol information.
24-Aug-05	Communication with the FDA regarding request for four recent PMA amendment titles from PMA Center

Date	Activity
25-Aug-05	MC forwarded e-mail to Dr. Love and requested further clarification on CDER communication to CDRH
25-Aug-05	Howard Holstein forwarded BMTI's e-mail from August 23 to Les Weinstein and Thinh Nguyen regarding problems with CBER.
26-Aug-05	FDA responded to BMTI email of August 23 and provided clarification
29-Aug-05	BMTI submits revised Package Insert and Summary of Safety and Effectiveness
30-Aug-05	BMTI submits electronic PDF copy of PMA Amendment A041 sent to A. Blackwell of FDA.
30-Aug-05	BMTI e-mailed Dr. Runner with the updated version of the SS&E and Package Insert
01-Sep-05	BMTI e-mailed Dr. Runner as a follow-up to the September 1, 2005 teleconference call on the Package insert.
07-Sep-05	H. Holstein of Hogan & Hartson L.L.P e-mailed Les Weinstein of CDRH inquiring of delay for PMA approval
07-Sep-05	FDA e-mailed BMTI verifying that the September 7th teleconference call would satisfy as the weekly update.
09-Sep-05	BMTI responded to FDA's request, via e-mail, on the lot traceability table from BMTI supplier
10-Sep-05	BMTI e-mailed Tim Ulatowski of FDA asking if there were any concerns since Tim would now have direct involvement of PMA approval process.
12-Sep-05	BMTI responded to Dr. FDA Sept. 7 email and updated Dr. Love and Dr. Runner of BMTI supplier's action on revising the table.
20-Sep-05	BMTI e-mailed Drs. Runenr & Love informing them that BMTI would remove supplier's facility from the PMA
20-Sep-05	A. Blackwell e-mailed BMTI requesting a photo of cup and syringe components
20-Sep-05	BMTI submits revised Specifications; QC Modifications for rhPDGF-BB
20-Sep-05	BMTI-FDA follow-up to telephone call regarding exclusion of BMTI supplier's manufacturing facility
21-Sep-05	BMTI submits electronic PDF copy of PMA Amendment A043 to Dr. Kurt Stromberg of FDA.
21-Sep-05	BMTI submits Electronic PDF copy of PMA Amendment A043 to A. Blackwell of FDA.
21-Sep-05	BMTI sent A. Blackwell a photo of cup and syringe components
22-Sep-05	BMTI responds to Kurt Stromberg via e-mail on agreed language for the SDS Page
23-Sep-05	BMTI submits revised Specifications; rhPDGF-BB Component
23-Sep-05	BMTI submitted a thank you e-mail to Drs. Runner & Love and Donna Tilman of the FDA on the approvable letter.

Date	Activity
23-Sep-05	BMTI submitted a thank you e-mail to A. Blackwell on the approvable letter and attached a copy of the amendment (A044) on the revised specifications.
23-Sep-05	BMTI submitted new SDS language (revised specs) to K. Stromberg and E. Shacter of FDA via e-mail
23-Sep-05	Letter from FDA for PMA P040013 was recommend by the FDA as approvable
23-Sep-05	Angela Blackwell (FDA) notified BMTI of her travels and when she would finish up on the approval package.
28-Sep-05	BMTI forwarded Blackwell (FDA) 9/23 email to Susan Runner (FDA) for further guidance on next steps to approval
28-Sep-05	BMTI submitted electronic PDF copy of PMA Amendment A044 to Dr. Kurt Stromberg of FDA.
28-Sep-05	BMTI submits electronic PDF copy of PMA Amendment A044 to A. Blackwell of FDA.
06-Oct-05	BMTI e-mailed and fed ex copy of the revised release specification as a follow-up to the approvable letter
06-Oct-05	Conference call with FDA regarding additional information in formal letter tying agreement to the conditions of approvaable letter
31-Oct-05	BMTI e-mailed Dr. Tillman of FDA asking for further information to expedite PMA approval process
04-Nov-05	BMTI responded to FDA package insert changes identifying concerns with FDA's changes
04-Nov-05	BMTI e-mailed FDA requesting further clarification as to why the meta-analysis was removed from the Package Insert.
04-Nov-05	Angela Blackwell (FDA) submitted package insert with changes.
07-Nov-05	Angela Blackwell responded to BMTI's inquiries on angiogenesis.
07-Nov-05	BMTI replied to FDA response regarding angiogenesis by providing FDA with scientific references showing that PDGF facilitates angiogenesis.
09-Nov-05	E-mail correspondence with Keisha Thomas and Vertleen Covington to schedule a compliance audit for PMA 040013.

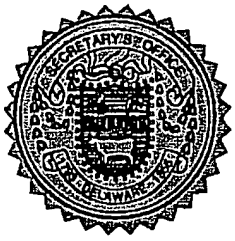
14

Delaware

The First State

I, HARRIET SMITH WINDSOR, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THAT THE SAID "BIOMIMETIC PHARMACEUTICALS, INC.", FILED A CERTIFICATE OF AMENDMENT, CHANGING ITS NAME TO "BIOMIMETIC THERAPEUTICS, INC.", THE FIFTH DAY OF AUGUST, A.D. 2005, AT 7:53 O'CLOCK P.M.

AND I DO HEREBY FURTHER CERTIFY THAT THE AFORESAID CORPORATION IS DULY INCORPORATED UNDER THE LAWS OF THE STATE OF DELAWARE AND IS IN GOOD STANDING AND HAS A LEGAL CORPORATE EXISTENCE NOT HAVING BEEN CANCELLED OR DISSOLVED SO FAR AS THE RECORDS OF THIS OFFICE SHOW AND IS DULY AUTHORIZED TO TRANSACT BUSINESS.



Harriet Smith Windsor

Harriet Smith Windsor, Secretary of State

3394448 8320

AUTHENTICATION: 4081005

050657582

DATE: 08-09-05

Delaware

The First State

I, HARRIET SMITH WINDSOR, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF AMENDMENT OF "BIOMIMETIC PHARMACEUTICALS, INC.", CHANGING ITS NAME FROM "BIOMIMETIC PHARMACEUTICALS, INC." TO "BIOMIMETIC THERAPEUTICS, INC.", FILED IN THIS OFFICE ON THE FIFTH DAY OF AUGUST, A.D. 2005, AT 7:53 O'CLOCK P.M.

A FILED COPY OF THIS CERTIFICATE HAS BEEN FORWARDED TO THE KENT COUNTY RECORDER OF DEEDS.

Harriet Smith Windsor

Harriet Smith Windsor, Secretary of State

3394448 8100

AUTHENTICATION: 4080589

050649698

DATE: 08-09-05

CERTIFICATE OF AMENDMENT TO
CERTIFICATE OF INCORPORATION
OF
BIOMIMETIC PHARMACEUTICALS, INC.

BioMimetic Pharmaceuticals, Inc., a corporation organized and existing under the General Corporation Law of the State of Delaware (the "Corporation"), does hereby certify:

FIRST: The Certificate of Incorporation of the Corporation is hereby amended by striking Article I in its entirety and replacing therefor the following:

I.

The name of the corporation (hereinafter called the "Corporation") is BioMimetic Therapeutics, Inc.

SECOND: The foregoing amendment was adopted by the Corporation's Board of Directors and Stockholders on August 5, 2005.

THIRD: This Certificate of Amendment is filed by authority of the duly elected Board of Directors and Stockholders in accordance with Sections 228 and 242 of the General Corporation Law of the State of Delaware.

IN WITNESS WHEREOF, this Certificate of Amendment has been executed by the Corporation's authorized officer this 5th day of August, 2005.

BIOMIMETIC PHARMACEUTICALS, INC.

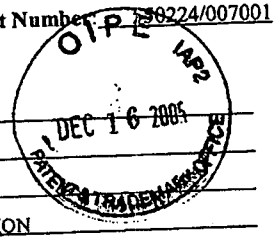
By: /s/Samuel E Lynch
Samuel E. Lynch
President and Chief Executive Officer

State of Delaware
Secretary of State
Division of Corporations
Delivered 08:02 PM 08/05/2005
FILED 07:53 PM 08/05/2005
SRV 050649698 - 3394448 FILE

153216-1

PROSECUTION

Attorney Docket Number: 730224/007001



The U.S. PTO date stamp sets forth the date of receipt of:

Applicant/Patentee: Antoniades et al.

Serial/Patent Number: 5,124,316

Filed/Issued: June 23, 1992

Title: METHOD FOR PERIODONTAL REGENERATION

☒ Transmittal Letter	Pages: 2	☐ Declaration & POA	Pages: ____
☐ Notice to File Missing Parts	Pages: ____	☐ Assignment & Cover Sheet	Pages: ____
☐ Reply to Missing Parts	Pages: ____	☐ Change of Address	Pages: ____
☐ Reply to Office Action	Pages: ____	☐ Preliminary Amendment	Pages: ____
☐ Petition for Extension	Pages: ____	☐ IDS	Pages: ____
☐ Drawings Formal/Informal	Pages: ____	☐ Sequence Listing	Pages: ____
☐ M-Fee Payment	Pages: ____	☐ Sequence Statement	Pages: ____
☐ Issue Fee Transmittal Form	Pages: ____	☐ Sequence Diskette	Number: ____
☒ Check	$: 1,120.00	☐ Application Data Sheet	Pages: ____

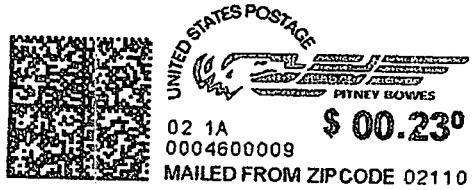
☒ Other Application for Extension of Patent Term under 35 U.S.C. 156 Pages: 17

☐ Other Exhibits 1-14 Pages: 86

☐ Other Certificate under 37 C.F.R. 3.73 (b) Pages: 14

☒ Other Five Certified Copies of Application Pages: 585

Atty/Secy: PTC/RTA/alp Matter Name: EV 768762375 US Date: 12/16/2005



CLARK & ELBING LLP
101 FEDERAL ST 15TH FLOOR
BOSTON MA 02110

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CLARK & ELBING LLP

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PATENT
ATTORNEY DOCKET NO. 50224/007001

Certificate of Mailing: EV768762375US Date of Deposit: December 16, 2005

I hereby certify under 37 C.F.R. § 1.10 that this correspondence is being deposited with the United States Postal Service as "**Express Mail Post Office to Addressee**" with sufficient postage on the date indicated above and is addressed to Mail Stop Patent Ext., Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Alis De La Cruz

Printed name of person mailing correspondence Signature of person mailing correspondence

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Antoniades et al.	Art Unit:	1809
Serial No.:	07/582,332	Examiner:	F. T. Moezie
Filed:	Sept. 13, 1990	Customer No.:	21559
Patent No.:	5,124,316		
Issued:	June 23, 1992		
Title:	METHOD FOR PERIODONTAL REGENERATION		

Mail Stop Patent Ext.
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

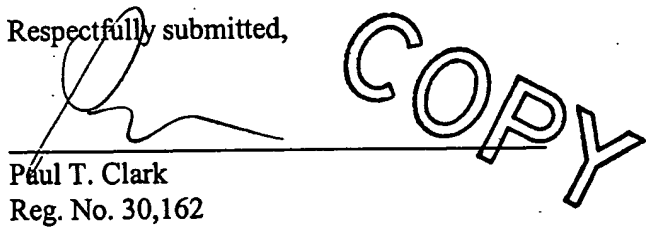
TRANSMITTAL LETTER

Applicants enclose the following documents:

1. Application for Extension of Patent Term Under 35 U.S.C. § 156;
2. Five Certified Copies of the Application for Extension of Patent Term Under 35 U.S.C. § 156, including the exhibits;
3. Exhibits 1-14;
4. Certificate Under 37 C.F.R. § 3.73(b)
5. A check in the amount of $1,120.00; and
6. A return post card.

If there are any other charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,



Date: Apr. 16, 2005

Paul T. Clark
Reg. No. 30,162

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045

COPY

PATENT
ATTORNEY DOCKET NO. 50224/007001

Certificate of Mailing

Date of Deposit: December 16, 2005 Label Number: EV 768762375 US

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Elvis DeLaCruz
Printed name of person mailing correspondence

Signature of person mailing correspondence

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Antoniades et al.	Art Unit:	1809
Serial No.:	07/582,332	Examiner:	F. T. Moezie
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Patent No.:	5,124,316		
Issued:	June 23, 1992		
Title:	METHOD FOR PERIODONTAL REGENERATION		

Mail Stop Patent Ext.
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

In accordance with 35 U.S.C. § 156 and 37 C.F.R 1.710(b)(3), Applicants, President and Fellows of Harvard College, a Massachusetts charitable corporation having a place of business at 17 Quincy Street, Cambridge, Massachusetts, 02138, and BioMimetic Therapeutics, Inc. (formerly BioMimetic Pharmaceuticals, Inc.), a Delaware corporation having a place of business at 389-A Nichol Mill Lane, Franklin, TN 37067, (hereinafter "Applicants"), represent that they are the assignees of the entire interest in and to U.S. Patent No. 5,124,316, granted to Harry N.

Antoniades and Samuel E. Lynch by virtue of assignments recorded at Reel 5027, Frame 0090 and Reel 5027, Frame 0089 on February 27, 1989 (EXHIBIT 4), and an assignment executed on November 4, 2005 and filed on November 29, 2005 (EXHIBIT 5).

Applicants, through undersigned counsel, hereby apply for a 2.7 year (987 day) extension of the term of U.S. Patent No. 5,124,316 under 35 U.S.C. § 156 on the basis of the following information submitted in accordance with the provisions of Title 37 C.F.R. § 1.740(a)(1)-(15), set forth in the sequence of those subparagraphs. Filed herewith is a Certificate under 37 C.F.R. § 3.73(b) and a Power of Attorney authorizing the undersigned to file and prosecute this Application for Extension of Patent Term, and to transact all business in relation thereto.

(1) Complete identification of the approved product by appropriate chemical and generic name, physical structure or characteristics

As a medical device[1], the approved product qualifies for patent term extension under 37 C.F.R 1.710(b)(3). In particular, the product is Biomimetic Therapeutics' synthetic grafting system for bone and periodontal regeneration. The system combines: (1) synthetic beta-tricalcium phosphate ([$Ca_3(PO_4)$]; hereinafter "β-TCP"), a highly porous bone void filler that serves as the osteoconductive matrix; and (2) highly purified, recombinant human platelet-derived growth factor composed of two disulfide-linked B-chain polypeptides (hereinafter "rhPDGF-BB"), which serves to enhance the physical properties of β-TCP by promoting bone and ligament cell proliferation (mitogenesis), cell migration (chemotaxis) into the wound and matrix, and revascularization (angiogenesis) of the surgical site.

1 As discussed below, the product was reviewed by the FDA as a combination product whose primary mode of action is its medical device component.

The system is marketed under the tradename "*GEM 21S*® Growth-factor Enhanced Matrix," and is provided as a kit containing (1) a container of 0.5 cc of β-TCP particles (0.250 to 1.0 mm); and (2) a solution of 0.5 ml rhPDGF-BB (0.3 mg/ml in a sodium acetate buffer) contained in a syringe. All of the components are supplied sterile. The product is prepared for use by fully saturating the β-TCP with the rhPDGF-BB solution. Following the preparation of a tissue flap to expose the osseous defect and thorough debridement and root planing of the osseous defect, the prepared product is packed into the osseous defect. The tissue flap is secured with interdental sutures to achieve complete coverage of the surgical site, and the damaged bone is allowed to regrow.

(2) A complete identification of the federal statute including the applicable provision of law under which the regulatory review occurred

GEM 21S® Growth-factor Enhanced Matrix was reviewed as a combination product and the federal statute under which the regulatory review occurred is § 503(g) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 353(g)). In accordance with the provisions of §503(g), the U.S. Food and Drug Administration determined that in view of the primary mode of action of *GEM 21S*®, the product was further reviewed as a class III medical device under § 515 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 360(e)).

(3) The date on which the product received permission for commercial marketing or use under the provision of law which the applicable regulatory review period occurred

The Pre-Marketing Application (PMA) under 21 U.S.C. §§ 353(g) and 360(e) for the *GEM 21S®* product was approved on November 18, 2005. (EXHIBIT 6)

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved

GEM 21S® Growth-factor Enhanced Matrix is not a drug product, but was classified by the Food and Drug Administration ("FDA") as a combination product in that it includes both a drug component (rh-PDGF-BB) and a medical device component (β-tricalcium phosphate particulate (β-TCP)). Because the FDA concluded that the primary mode of action of *GEM 21S®* is the medical device component (β-TCP), *GEM 21S®* was reviewed by the FDA as a class III medical device.

Two different formulations of rh-PDGF-BB were previously reviewed by the FDA – Becaplermin and Regranex® Gel. Becaplermin is a bulk rh-PDGF-BB product manufactured by Chiron Corporation and is provided as a bulk raw material. Becaplermin was reviewed by the FDA as a biological product (and not as a drug or combination product) under the Public Health Service Act (42 U.S.C. § 262). Becaplermin Concentrate was reviewed under BLA No. 96-1422; Biologics License No. 1106 and was approved on December 16, 1997. (EXHIBIT 7) Becaplermin Concentrate was only approved for manufacture under a shared manufacturing

arrangement with OMJ Pharmaceuticals, Inc., and was not approved for commercial marketing to clinicians for use in its bulk formulation.

Regranex Gel is manufactured by OMJ Pharmaceuticals, and is a non-sterile, low bioburden, preserved, sodium carboxymethylcellulose based (CMC) topical gel, containing 100μg of Becaplermin per gram of gel. Regranex Gel was approved for commercial marketing as a biological product (and not as a drug or combination product) under the Public Health Service Act (42 U.S.C. § 262). Regranex Gel was reviewed by the FDA under Biologics License Application (BLA) No. 96-1408; Biologics License No. 1196 was approved on December 16, 1997. (EXHIBIT 7) Regranex Gel was approved for treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have adequate blood supply. The package insert label for Regranex/Becaplermin is included herewith as EXHIBIT 8.

Applicants note that the regulatory review of Regranex/Becaplermin was the basis for extending the term of U.S. patent 4,845,075 (the "'075 patent") under 35 U.S.C. 156. A copy of the Application for Patent Extension for the '075 patent is attached hereto as EXHIBIT 9.

Applicants also note that other types of tricalcium phosphate medical devices have been approved by the FDA under 510(k) applications as Class II medical devices. However, the first β-TCP medical device to be approved for use in a dental application was reviewed as a Class III PMA product under the tradename Perio-Oss, and was approved for commercial use in 1981. (EXHIBIT 10) Since that time, β-TCP for dental use has been reclassified as a Class II Medical Device and all other products have been cleared for commercial use via the 510(k) route. It is important to note that neither Perio-Oss, nor any of the other Class II tricalcium phosphate medical devices were reviewed as combination products pursuant to 21 U.S.C. § 353(g).

The β-TCP particulate included in *GEM 21S®* is supplied by Orthovita Company. Orthovita markets a variety of β-TCP products under the tradename Vitoss™. Vitoss™ particulate is a Class II Medical Device and the subject of 510(k) numbers K994337 and K032409, which were cleared on December 14, 2000 and August 29, 2003, respectively. Vitoss™ particulate is cleared for use as a bone void filler for voids or gaps that are not intrinsic to the stability of the bony structure, and for use in the treatment of surgically created osseous defects or osseous defects created from traumatic injury to the bone. The Vitoss particulate 510(k)'s are classified under product code MQV as orthopedic products, and it is not a dental product such as *GEM 21S®*. Various documents relating to the approval of Vitoss™ particulate 510(k)'s are included in EXHIBIT 11.

Despite the previous approvals of Becaplermin, Regranex and various tricalcium phosphate products, *GEM 21S®* is the first product containing either rh-PDGF-BB or β-TCP to be reviewed by the FDA under § 503(g) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 353(g)) as a combination product. Furthermore, *GEM 21S®* is the first product containing rh-PDGF-BB to be approved by the FDA under 21 U.S.C. § 360(e) as a class III medical device.

(5) Statement that the present application is being submitted within the sixty day period permitted for submission and an identification of the date of the last day on which the application could be submitted

The present application for patent term extension is being submitted within the sixty day period permitted for submission pursuant to 37 C.F.R. § 1.720(f). The last day for submission of the present application is January 17, 2006.

(6) The complete identification of the patent for which an extension is being sought by the name of the inventors, the patent number, the date of issue, and the expiration date

The present application for extension is for U.S. Patent No. 5,124,316 (U.S. Serial No. 07/582,332) issued on June 23, 1992 and expiring on June 23, 2009. The inventors are Harry N. Antoniades and Samuel E. Lynch.

(7) A copy of the entire patent for which extension is being sought, including the entire specification, claims, and drawings

A copy of U.S. Patent No. 5,124,316 is attached as (EXHIBIT 1).

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent

Receipts of maintenance fee payments for U.S. Patent No. 5,124,316 for the after-grant periods of 3½, 7½, and 11½ years are attached as EXHIBIT 2. A copy of the Certificate of Correction issued in connection with U.S. Patent No. 5,124,316 is attached as EXHIBIT 3. No disclaimer or reexamination certificate has been issued in connection with U.S. Patent No. 5,124,316.

(9) Statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on a method of using the approved product

U.S. Patent No. 5,124,316 includes only one claim, which reads:

A method of promoting growth of damaged bone, periodontium, or ligament of a living mammal, comprising the steps of

producing a surgical flap of skin to expose said damaged bone, periodontium, or ligament,

planing said damaged bone or periodontium to remove organic matter from said bone or periodontium

applying platelet derived growth factor in a pharmaceutically acceptable carrier to said exposed bone, periodontium, or ligament,

replacing said flap, and

allowing said damaged bone, periodontium, or ligament to regrow.

The approved product, "*GEM 21S®*," is a system for treating periodontally-related bone defects. A copy of the approved package insert is attached hereto as EXHIBIT 12. As indicated in the package insert, *GEM 21S®* is composed of two sterile components:

(1) Synthetic beta-tricalcium phosphate (ß-TCP) [Ca3 (PO4)], which is a highly porous, resorbable osteoconductive scaffold or matrix that provides a framework for bone ingrowth, and

(2) Highly purified, recombinant human platelet-derived growth factor-BB (rhPDGF-BB).

In addition, as reflected in the package insert, *GEM 21S®* is indicated to treat the following periodontally-related defects:

- Intrabony periodontal defects;
- Furcation periodontal defects; and
- Gingival recession associated with periodontal defects.

The following table illustrates how the surgical technique as outlined in the *GEM 21S®* package insert practices the invention claimed in the '316 patent. This table is provided merely for illustrative purposes as a single embodiment covered by claim 1 of the '316 patent, and is not intended to in any way restrict the interpretation of claim 1 with regard to other embodiments:

'316 Claim	*GEM 21S®* Surgical Techniques
producing a surgical flap of skin to expose said damaged bone, periodontium, or ligament	Following exposure of the defect with a full thickness mucoperiosteal flap, all granulation tissue must be carefully removed.
planing said damaged bone or periodontium to remove organic matter from said bone or periodontium	Thorough soft tissue debridement of the defect is critical to successful regeneration. Granulation tissue, if left in the defect, could be stimulated by the rhPDGF-BB component, diminishing the desired regenerative response. Exposed tooth root surfaces should also be thoroughly planed.
applying platelet derived growth factor in a pharmaceutically acceptable carrier to said exposed bone, periodontium, or ligament	Following thorough debridement of the osseous defect, the clinician, based on his or her experience, estimates the amount of *GEM 21S®* needed to fill the defect. For best results, *GEM 21S®* must completely fill the defect to the level of the surrounding bony walls. Overfilling should be avoided. The clinician prepares the *GEM 21S®* graft by fully saturating the ß-TCP particles with the rhPDGF-BB solution and letting the product sit for approximately ten (10) minutes. Proper aseptic technique must be employed in preparing and applying *GEM 21S®*. The saturated *GEM 21S®* should be placed into the defect using moderate pressure, taking care not to crush the particles. In order to enhance the formation of new bone, *GEM 21S®* should be placed in direct contact with well-vascularized bone. Excessive bleeding should be controlled prior to placing grafting materials.
replacing said flap	Following placement of the *GEM 21S®* and completion of any additional surgical steps, the mucoperiosteal flaps should be sutured to achieve primary closure wherever possible.
allowing said damaged bone, periodontium, or ligament to regrow	Postoperative patient management should follow the same regimen as similar cases utilizing autogenous bone grafting. Pre-requisites for all regenerative procedures include prevention of wound dehiscence, a stable clot and minimal bacterial contamination.

Thus, claim 1 reads on the approved method of using *GEM 21S®*.

(10) The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period, as set forth in 37 C.F.R. § 1.740(a)(10)(v):

A) The effective date of the investigational device exemption (IDE) and the IDE number, if applicable

An IDE (No. 6010340) for *GEM 21S®* was conditionally approved on February 28, 2002. This conditional approval permitted initiation of patient enrollment in the *GEM 21S®* pivotal clinical study. The IDE was given final approval on April 24, 2002.

B) The date on which the application for product approval or notice of completion of a product development protocol under § 515 of the Federal Food, Drug and Cosmetic Act was initially submitted and the number of the application

1) A Pre-market Approval application (PMA) for *GEM 21S®* was submitted on March 12, 2004.

2) The PMA number is P040013.

C) The date on which the application was approved or the protocol declared to be completed

The *GEM 21S®* PMA was approved on November 18, 2005.

(11) Brief description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities

A brief description of the significant activities undertaken by the marketing applicant, Biomimetic Therapeutics, Inc, and the applicable dates are provided in chronological order as EXHIBIT 13. It should be noted that the IDE and PMA for *GEM 21S*® were filed in the name of BioMimetic Pharmaceuticals, Inc. In August 2005, Biomimetic Pharmaceuticals, Inc. changed its name to BioMimetic Therapeutics, Inc., the current applicant hereunder and co-owner of the '316 patent. A copy of the certificate of name change is attached hereto as EXHIBIT 14.

(12) Statement that in the opinion of the applicant the patent is eligible for extension and a statement as to the length of extension claimed, including how the extension was calculated

Applicants are of the opinion that U.S. Patent No. 5,124,316 is eligible for extension under 35 U.S.C. § 156 because it satisfies all the requirements for such an extension in as much as:

(i) the term of such patent has not expired before submission of this application (35 U.S.C. § 156(a)(1));

(ii) the term of such patent has never been extended (35 U.S.C. § 156(a)(2));

(iii) the application for extension is submitted by the owners of record, through undersigned counsel, in accordance with the requirements of 35 U.S.C. § 156(d) (35 U.S.C. § 156(a)(3));

(iv) the approved product, *GEM 21S®*, has been subject to a regulatory review period before its commercial marketing or use (35 U.S.C. § 156(a)(4));

(v) the permission for the commercial marketing or use of the product, *GEM 21S®*, after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of the Federal Food, Drug and Cosmetic Act under which such regulatory review period occurred (35 U.S.C. § 156(a)(5)); and

(vi) no other patent has been extended for the same regulatory review period for the approved product (35 U.S.C. § 156(c)(4)).

As noted above, components of *GEM 21S®* (Becaplermin and Vitoss) were previously approved for commercial marketing, but such approvals were for different "products" and were

under different statutory provisions than the statutory provisions under which the *GEM 21S®* regulatory review period occurred.

In particular, Becaplermin/Regranex was reviewed by the FDA under the provision of the Federal Food, Drug and Cosmetic Act relating to biological products (42 U.S.C. § 262). (See Application for Extension of Patent Term of US Patent 4,845,075, page 3, paragraph 2 (EXHIBIT 9).) Vitoss was reviewed under a 510(k) application as a class II medical device. (EXHIBIT 11) In contrast, the *GEM 21S®* product was reviewed by the FDA under 21 U.S.C. § 353(g) as a combination product, and in view of its primary mode of action was also reviewed under 21 U.S.C. §360(e) as a class III medical device.

Applicants submit that Becaplermin/Regranex and Vitoss are clearly different "products" as that term is used in 35 U.S.C. § 156(a)(5). Moreover, even if they were the same "product," *GEM 21S®* was reviewed under different statutory provisions. Therefore, the *GEM 21S®* product "is the first permitted commercial marketing or use of the *product under the provision of the Federal Food, Drug and Cosmetic Act under which such regulatory review period occurred*" as required under 35 U.S.C. § 156(a)(5) (emphasis added).

Applicants request an extension of the patent term of U.S. Patent No. 5,124,316 by 2.7 years (987 days) from the original expiration date of June 23, 2009 to March 6, 2012. This period of extension is calculated pursuant to 37 C.F.R. § 1.777 as follows:

Calculation of Patent Term Extension For a Medical Device Under 37 C.F.R. § 1.777

Conditional Approval of IDE			February 28, 2002
PMA Filed March 12, 2004		(c)(1)	743 days
PMA Approved November 18, 2005		(c)(2)	616 days
Reg. Rev. Period	Total		1359 days
The subject patent issued June 23, 1992 before the IDE was filed		(d)(1)(i)	0 days
Applicants acted with due diligence at all relevant times		(d)(1)(ii)	0 days
One-half the number of days remaining in the Period defined by (c)(1) after being reduced by (d)(1)(i) $\frac{743-0}{2}$ = (d)(1)(iii)			371 days
Regulatory Review Period: 1359 – 371 =			987 days
Original patent issued June 23, 1992 and is set to expire June 23, 2009 plus 987 days		(d)(2)	March 6, 2012
PMA Approval October 1, 2005 + 14 years		(d)(3)	October 1, 2019
Earlier of (d)(2) and (d)(3)		(d)(4)	March 6, 2012
Original issue date June 23, 2009 + 5 years		(d)(5)(i)	June 23, 2014
Earlier of date obtained pursuant to (d)(4) and (d)(5)(i)		(d)(5)(ii)	March 6, 2012
The original patent was issued after September 24, 1984		(d)(6)(i) (d)(6)(ii)	N/A N/A

Applicants respectfully submit that U.S. Patent No. 5,124,316 is eligible for a 987 day extension as calculated pursuant to 37 C.F.R. § 1.777. Therefore, Applicants respectfully request that the original expiration date of the patent be extended to March 6, 2012.

(13) Statement that the Applicants acknowledge a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension

Applicants, through undersigned counsel, acknowledge a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determinations to be made relative to the application for extension, in accordance with 37 C.F.R. § 1.765.

(14) The prescribed fee for receiving and acting upon the application for extension

A check in the amount of $1,120.00 for payment of the patent term extension application fee, pursuant to 37 C.F.R. § 1.20(j)(1) is enclosed. If there are any other charges or any credits, please apply them to Deposit Account No. 03-2095.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed

Please direct all inquiries and correspondence relating to this application for patent term extension to:

Paul T. Clark

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045

Respectfully submitted,

Date: Aug. 16, 2005

Paul T. Clark
Reg. No. 30,162

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045

COPY

PATENT

ATTORNEY DOCKET NO. 50224/007001

Certificate of Mailing

Date of Deposit: 12/16/05 Label Number: EV 708762375 US

I hereby certify under 37 C.F.R. § 1.10 that this correspondence is being deposited with the United States Postal Service as "Express Mail Post Office to Addressee" with sufficient postage on the date indicated above and is addressed to Mail Stop Patent Ext., Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Elvis De La Cruz
Printed name of person mailing correspondence

Signature of person mailing correspondence

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Antoniades et al.	Art Unit:	1809
Serial No.:	07/582,332	Examiner:	F. T. Moezie
Filed:	Sept. 13, 1990	Customer No.:	21559
Patent No.:	5,124,316		
Issued:	June 23, 1992		
Title:	METHOD FOR PERIODONTAL REGENERATION		

Mail Stop Patent Ext.
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE UNDER 37 C.F.R. § 3.73(b)

Pursuant to 37 C.F.R. § 3.73(b), President and Fellows of Harvard College, a Massachusetts charitable corporation having a place of business at 17 Quincy Street, Cambridge, Massachusetts, 02138, and BioMimetic Therapeutics, Inc., a Delaware corporation having a place of business at 389-A Nichol Mill Lane, Franklin, TN, certify that they are the assignees of the entire right, title, and interest in the above-captioned patent identified above.

Pursuant to 37 C.F.R. § 3.73(b)(2), this Certificate is signed by an attorney of record authorized to act on behalf of the assignees.

Pursuant to 37 C.F.R. § 3.73(b)(1)(ii), the undersigned attorney of record certifies that President and Fellows of Harvard College, a charitable corporation, and BioMimetic Therapeutics, Inc., a corporation, are the assignees of the entire right, title, and interest in the patent by virtue of:

An assignment from the inventors of the application. The assignment was Recorded in the U.S. Patent and Trademark Office at Reel/Frame 5027/0089 and 5027/0090 on February 27, 1989; copies of the executed assignments and notices of recordation are attached hereto; and

An assignment from the Institute of Molecular Biology executed on November 4, 2005 and filed with the U.S. Patent and Trademark Office on November 29, 2005; a copy of the executed assignment is attached hereto.

The undersigned has reviewed all the documents in the chain of title of the patent identified above and, to the best of undersigned's knowledge and belief, title is in the assignees identified above. The undersigned (whose title is supplied below) is empowered to act on behalf of the assignees.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity

of the application or any patents issued thereon.

Respectfully submitted,

COPY

Date: Dec. 16, 2005

Paul T. Clark
Reg. No. 30,162

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045

ASSIGNMENT

For valuable consideration, I, Samuel (FIRST) E. (MIDDLE INITIAL) Lynch (LAST)

of Jamaica Plain (CITY OR TOWN), Massachusetts (STATE) hereby assign

to THE PRESIDENT AND FELLOWS OF HARVARD COLLEGE, a

Massachusetts corporation having a place of business

at Cambridge, Massachusetts,

and its successors and assigns (collectively hereinafter called "the Assignee"), the entire right, title and interest throughout the world in the inventions and improvements which are the subject of an application for United States ~~Patent signed herewith~~ Serial No. 299,763 filed January 20, 1989 ~~(DATE)~~, entitled WOUND HEALING

this assignment including said application, any and all United States and foreign patents granted for any of said inventions or improvements, and the right to claim priority based on the filing date of said application under the International Convention for the Protection of Industrial Property, the Patent Cooperation Treaty, the European Patent Convention, and all other treaties of like purposes; and I authorize the Assignee to apply in all countries in my name or in its own name for patents and like rights of exclusion and for inventor's certificates for said inventions and improvements; and I agree for myself and my heirs, legal representatives and assigns, without further compensation to perform such lawful acts and to sign such further applications, assignments, Preliminary Statements and other lawful documents as the Assignee may reasonably request to effectuate fully this assignment.

In Witness Whereof, I hereto set my hand and seal at Boston, Massachusetts, this 17 day of February, 1989.

/s/ Samuel E. Lynch L.S.

Samuel (FIRST) E. (MIDDLE INITIAL) Lynch (LAST)

State of Massachusetts :
ss.
County of Suffolk :

Before me this 17 day of February, 1989, personally appeared Samuel E. Lynch known to me to be the person whose name is subscribed to the foregoing Assignment and acknowledged that he executed the same as his free act and deed for the purposes therein contained.

/s/ Deborah A. McKenzie
Notary Public

[Notary's seal here]

My commission expires: Nov. 16, 1995

RECORDED
PATENT & TRADEMARK OFFICE
FEB 27 89

/s/ Arthur E. Kluge
COMMISSIONER OF PATENTS
UNITED STATES PATENT OFFICE

REEL 5027, FRAME 089

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

TO: PAUL T. CLARK
FISH & RICHARDSON
STE 2500
ONE FINANCIAL CENTER
BOSTON, MA 02111-2658

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME NUMBER REFERENCED BELOW. A DIGEST OF THE DOCUMENT HAS ALSO BEEN MADE AND APPEARS IN THE OFFICE'S RECORDS AS SHOWN:

ASSIGNOR: 001 ANTONIADES, HARRY N. DOC DATE: 02/17/89

RECORDATION DATE: 02/27/89 NUMBER OF PAGES 001 REEL/FRAME 5027/0090

DIGEST: ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE: 501 INSTITUTE OF MOLECULAR BIOLOGY, THE, BOSTON, MA., A DE. CORP.

SERIAL NUMBER 7-299763 FILING DATE 01/23/89
PATENT NUMBER ISSUE DATE 00/00/00

TITLE OF INVENTION: WOUND HEALING

INVENTOR: 001 ANTONIADES, HARRY N.
INVENTOR: 002 LYNCH, SAMUEL E.

ASSIGNMENT

For valuable consideration, I, Harry (FIRST) N. (MIDDLE INITIAL) Antoniades (LAST)

of Newton (CITY OR TOWN), Massachusetts (STATE) hereby assign

to THE INSTITUTE OF MOLECULAR BIOLOGY, Inc., a

Delaware corporation having a place of business

at Boston, Massachusetts,

and its successors and assigns (collectively hereinafter called "the Assignee"), the entire right, title and interest throughout the world in the inventions and improvements which are the subject of an application for United States ~~Patent~~ Serial No. 299,763 filed January 20, 1989 ~~this day~~, entitled WOUND HEALING

this assignment including said application, any and all United States and foreign patents granted for any of said inventions or improvements, and the right to claim priority based on the filing date of said application under the International Convention for the Protection of Industrial Property, the Patent Cooperation Treaty, the European Patent Convention, and all other treaties of like purposes; and I authorize the Assignee to apply in all countries in my name or in its own name for patents and like rights of exclusion and for inventor's certificates for said inventions and improvements; and I agree for myself and my heirs, legal representatives and assigns, without further compensation to perform such lawful acts and to sign such further applications, assignments, Preliminary Statements and other lawful documents as the Assignee may reasonably request to effectuate fully this assignment.

In Witness Whereof, I hereto set my hand and seal at Boston, Massachusetts, this 17 day of February, 1989.

Harry N. Antoniades L.S.
(FIRST) Harry (MIDDLE INITIAL) N. (LAST) Antoniades

State of Massachusetts :
ss.
County of Suffolk :

Before me this 17 day of February, 19 89, personally appeared Harry N. Antoniades known to me to be the person whose name is subscribed to the foregoing Assignment and acknowledged that he executed the same as his free act and deed for the purposes therein contained.

Deborah C. McIlmoyle
Notary Public

[Notary's seal here]

My commission expires: Nov 16, 1995

RECORDED
PATENT & TRADEMARK OFFICE
FEB 27 89

COMMISSIONER OF PATENTS
AND TRADEMARKS OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

TO: PAUL T. CLARK
FISH & RICHARDSON
STE 2500
ONE FINANCIAL CENTER
BOSTON, MA 02111-2658

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME NUMBER REFERENCED BELOW. A DIGEST OF THE DOCUMENT HAS ALSO BEEN MADE AND APPEARS IN THE OFFICE'S RECORDS AS SHOWN:

ASSIGNOR: 001 LYNCH, SAMUEL E. DOC DATE: 02/17/89

RECORDATION DATE: 02/27/89 NUMBER OF PAGES 001 REEL/FRAME 5027/0089

DIGEST: ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE: 501 PRESIDENT AND FELLOWS OF HARVARD COLLEGE, THE, CAMBRIDGE, MA., A MA. CORP.

SERIAL NUMBER 7-299763 FILING DATE 01/23/89
PATENT NUMBER ISSUE DATE 00/00/00

TITLE OF INVENTION: WOUND HEALING

INVENTOR: 001 ANTONIADES, HARRY N.
INVENTOR: 002 LYNCH, SAMUEL E.

ASSIGNMENT

For valuable consideration, we,

Full Name of Assignor	City	State (and Country if not USA)
Institute of Molecular Biology, Inc.	Delaware	P.O. Box 4278 Shrewsbury, MA 01545

hereby assign to

Full Name of Assignee	State of Incorporation	Business Address
BioMimetic Therapeutics, Inc.	Delaware	389 Nichol Mill Lane Franklin, TN 37067

and to its successors and assigns (collectively hereinafter called "the Assignee"), the entire right, title, and interest throughout the world in the inventions and improvements which are the subject of one or more of the patents and applications listed on Schedule A, which is attached hereto.

This assignment includes the patents and applications listed in the attached Schedule A, any and all United States and foreign patents, utility models, and design registrations granted for any of said inventions or improvements, and the right to claim priority based on the filing date of any of the patents and applications listed in the attached Schedule A under the International Convention for the Protection of Industrial Property, the Patent Cooperation Treaty, the European Patent Convention, and all other treaties of like purposes; and we authorize the Assignee to apply in all countries in our names or in its own name for patents, utility models, design registrations, and like rights of exclusion, and for inventors' certificates for said inventions and improvements; and we agree for ourselves and our respective heirs, legal representatives and assigns, without further compensation, to perform such lawful acts and to sign such further applications, assignments, Preliminary Statements, and other lawful documents as the Assignee may reasonably request to effectuate fully this assignment.

IN WITNESS WHEREOF, I hereto set my hand and seal at SHREWSBURY/MASSACHUSETTS, this 4th day of NOVEMBER, 2005

John M. Naples L.S.

John M. Naples, President
Institute of Molecular Biology, Inc.

STATE OF MASSACHUSETTS :

:ss.

COUNTY OF WORCESTER :

Before me this 4th day of November, 2005, before me, the undersigned notary public, personally appeared John M. Naples, proved to me through satisfactory evidence of identification, which consisted of MASSACHUSETTS DRIVERS LICENSE, to be the person whose name is subscribed to the foregoing Assignment, and acknowledged that he executed the same as his free act and deed for the purposes therein contained.

Notary Public

My Commission Expires: 020708

[Notary's Seal Here]

PATRICIA MacISAAC
Notary Public
Commonwealth of Massachusetts
My Commission Expires
February 7, 2008

Schedule A
(Page 1 of 5)

C&E Ref No:	Status	Title	Application No:	Filed:	Patent No:	Issued:
02854-007001	Abandoned	WOUND HEALING AND BONE REGENERATION	06/930,762	14-Nov-1986		
02854-009001	Issued	WOUND HEALING AND BONE REGENERATION USING PDGF AND IGF-1	07/120,943	16-Nov-1987	4,861,757	29-Aug-1989
02854-010001	Issued	WOUND HEALING COMPOSITION OF TGF-ALPHA AND PDGF	07/136,399	22-Dec-1987	4,874,746	17-Oct-1989
02854-011001	Issued	WOUND HEALING USING IGF-I AND TGFβ	07/196,975	20-May-1988	4,983,581	8-Jan-1991
02854-011002	Abandoned	WOUND HEALING USING IGF-I AND TGFβ	07/530,649	30-May-1990		
02854-011003	Issued	WOUND HEALING USING IGF-II AND TGF	07/857,713	25-Mar-1992	5,256,644	26-Oct-1993
02854-012001	Issued	PROCESS OF WOUND HEALING USING PDGF AND EGF	07/231,145	10-Aug-1988	5,034,375	23-Jul-1991
02854-013003	Abandoned	WOUND HEALING	07/449,303	5-Dec-1989		
02854-013004	Abandoned	WOUND HEALING	07/639,060,303	9-Jan-1991		
02854-014001	Issued	WOUND HEALING USING PDGF AND IGF-II	07/272,090	16-Nov-1988	5,019,559	28-May-1991
02854-015001	Abandoned	WOUND HEALING	07/299,763	23-Jan-1989		
02854-015002	Issued	METHOD OF PERIDONTAL REGENERATION	07/582,332	13-Sep-1990	5,124,316	23-Jun-1992
02854-016001	Issued	WOUND HEALING COMPOSITION OF IL-1 AND PDGF OR IGF-1	07/403,969	7-Sep-1989	5,035,887	30-Jul-1991
02854-026001	Abandoned	BONE REGENERATION	07/799,375	27-Nov-1991		
02854-027001	Issued	NERVE REGENERATION	08/198,542	18-Feb-1994	6,506,727	14-Jan-2003
02854-033001	Issued	DEVICE TO PROMOTE DRUG-INDUCED NERVE REGENERATION	08/187,210	26-Jan-1994	5,656,605	12-Aug-1997
02854-034001	Issued	PYRIDINOLINE CROSSLINKS AS MARKERS OF PERIODONTAL AND PERI-IMPLANT DISEASE ACTIVITY	08/197,131	16-Feb-1994	5,516,699	14-May-1996

Schedule A
(Page 2 of 5)

C&E Ref No.	Country	Type	Status	Application No.	Filed	Patent No.	Issued
WOUND HEALING AND BONE REGENERATION							
02854-007AT 1	Austria	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007AU1	Australia	PCT	Granted	83289/87	13-Nov-1987	600069	02-Aug-1990
02854-007BE1	Belgium	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007CA1	Canada	PCT	Granted	551,909	16-Nov-1987	1,322,714	05-Oct-1993
02854-007CH1	Switzerland	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007CN1	China	PCT	Granted	87101250.2	14-Nov-1987	87101250.2	30-Oct-1994
02854-007DE1	Germany	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007DK1	Denmark	PCT	Granted	3932/88	13-Nov-1987	25-Jul-81	30-May-05
02854-007EP1	Europe	PCT	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007FR1	France	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007FR2	France	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-007GB1	Great Britain	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007IE1	Ireland	PCT	Granted	3075/87	13-Nov-1987	60517	20-Jul-1994
02854-007IT1	Italy	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007JP1	Japan	PCT	Granted	500179/87	13-Nov-1987	1868245	26-Aug-1994
02854-007KR1	Korea	PCT	Granted	88-700829	13-Nov-1987	106280	17-Oct-1996
02854-007LU1	Luxembourg	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007NL1	Netherlands	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007NZ1	New Zealand	PCT	Granted	222551	16-Nov-1987	222551	
02854-007SE1	Sweden	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007TW1	Taiwan	PCT	Granted	76107672	15-Dec-1987	NI-51493	30-Jan-1992
02854-007ZA1	South Africa	PCT	Granted	87/8566	16-Nov-1987	87/8566	26-Jul-1989
02854-007OA1	Africa (OAPI)	PCT	Abandoned	PV59385	13-Nov-1987	9159	31-Mar-1992
02854-007MX1	Mexico	PCT	Abandoned	930672	16-Nov-1987	170454	23-Aug-1993
02854-007NO1	Norway	PCT	Abandoned	88/3127	13-Nov-1987		
02854-007WO1	International	PCT	Expired	PCT/US87/02975	13-Nov-1987		
WOUND HEALING							
02854-010AT1	Austria	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010AU1	Australia	PCT	Granted	37472/89	20-Dec-1988	613776	03-Dec-1991
02854-010BE1	Belgium	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010CA1	Canada	PCT	Granted	586,562	21-Dec-1988	1,322,164	14-Sep-1993
02854-010CH1	Switzerland	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010CN1	China	PCT	Granted	88109273.8	21-Dec-1988	88109273.8	19-Jul-1994
02854-010DE1	Germany	EPC	Granted	89901681.0	20-Dec-1988	P3885300.0	27-Oct-1993
02854-010DK1	Denmark	PCT	Granted	4122/89	20-Dec-1988	175947	08-Aug-2005
02854-010EP1	Europe	PCT	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010FR1	France	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010GB1	Great Britain	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010IE1	Ireland	PCT	Granted	3833/88	21-Dec-1988	61283	14-Oct-1994
02854-010IT1	Italy	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010JP1	Japan	PCT	Granted	501944/89	20-Dec-1988	1923551	25-Apr-1995
02854-010LU1	Luxembourg	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010MX1	Mexico	PCT	Granted	14307	22-Dec-1988	164966	09-Oct-1992
02854-010NL1	Netherlands	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010NZ1	New Zealand	PCT	Granted	227429	21-Dec-1988	227429	14-May-1991
02854-010SE1	Sweden	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010TW1	Taiwan	PCT	Granted	78100693	01-Feb-1989	NI-51930	20-Feb-1992
02854-010ZA1	South Africa	PCT	Granted	88/9594	22-Dec-1988	88/9594	27-Sep-1989
02854-010OA1	Africa (OAPI)	PCT	Abandoned	PV59630	20-Dec-1988	9129	31-Oct-1991
02854-010KR1	Korea	PCT	Abandoned	89/701555	20-Dec-1988		
02854-010NO1	Norway	PCT	Abandoned	89/3346	20-Dec-1988		
02854-010RU1	Russian Federation	PCT	Abandoned	4742130.14	20-Dec-1988		
02854-010WO1	International	PCT	Expired	PCT/US88/04557	20-Dec-1988		

Schedule A
(Page 3 of 5)

C&E Ref No	Country	Type	Status	Application No	Filed	Patent No	Issued
WOUND HEALING							
02854-011AT1	Austria	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011AT2	Austria	EPC	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011BE1	Belgium	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011BE2	Belgium	EPC	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011CA2	Canada	PCT	Granted	2,082,420	30-May-1991	2082420	20-Jul-2004
02854-011CH1	Switzerland	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011CH2	Switzerland	EPC	Granted	91910904.1	30-May-1991	531425	14-Aug-2002
02854-011DE1	Germany	EPC	Granted	89906917.3	22-May-1989	P68917300.8	03-Aug-1994
02854-011DE2	Germany	EPC	Granted	69133087.5	30-May-1991	0531425	14-Aug-2002
02854-011DK2	Denmark	EPC	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011EP1	Europe	PCT	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
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02854-011ES2	Spain	EPC	Granted	0531425	30-May-1991	0531425	14-Aug-2002
02854-011FR1	France	EPC	Granted	0419534	22-May-1989	0419534	03-Aug-1994
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02854-011GB1	Great Britain	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
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02854-011GR2	Greece	EPC	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
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02854-011IT2	Italy	EPC	Granted	0531425	30-May-1991	0531425	14-Aug-2002
02854-011JP1	Japan	PCT	Granted	506485/89	22-May-1989	1924479	25-Apr-1995
02854-011JP2	Japan	PCT	Granted	3-510861	30-May-1991	3,377,524	06-Dec-2002
02854-011LI2	Liechtenstein	EPC	Granted	91910904.1	30-May-1991	531425	14-Aug-2002
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02854-011WO1	International	PCT	Expired	PCT/US89/02229	22-May-1989		
02854-011WO2	International	PCT	Expired	PCT/US91/03829	30-May-1991		
WOUND HEALING							
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02854-012BE1	Belgium	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012CA1	Canada	PCT	Granted	607,968	10-Aug-1989	1336816	29-Aug-1995
02854-012CH1	Switzerland	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012DE1	Denmark	EPC	Granted	89910545.6	10-Aug-1989	P68912758	26-Jan-1994
02854-012DE1	Germany	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012EP1	Europe	PCT	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012FR1	France	EPC	Granted	89910545.6	10-Aug-1989	382841	26-Jan-1994
02854-012GB1	Great Britain	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012IT1	Italy	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012JP1	Japan	PCT	Granted	509811/89	10-Aug-1989	1975393	27-Sep-1995
02854-012LU1	Luxembourg	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012NL1	Netherlands	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012SE1	Sweden	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012WO1	International	PCT	Expired	PCT/US89/03490	10-Aug-1989		

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C & E Ref. No.	Country	Type	Status	Application No.	Filed	Patent No.	Issued
WOUND HEALING USING PDGF AND IGF-II							
02854-014AT1	Austria	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014BE1	Belgium	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014CA1	Canada	PCT	Granted	2,060,208	10-Apr-1990	2,060,208	20-Feb-2001
02854-014CH1	Switzerland	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014DE1	Germany	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014DK1	Denmark	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014EP1	Europe	PCT	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014ES1	Spain	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014FR1	France	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014GB1	Great Britain	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014IT1	Italy	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014JP1	Japan	PCT	Granted	507475/90	10-Apr-1990	2030420	19-Mar-1996
02854-014LU1	Luxembourg	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014NL1	Netherlands	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014SE1	Sweden	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014WO1	International	PCT	Expired	PCT/US90/01936	10-Apr-1990		
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02854-016EP1	Europe	PCT	Abandoned	90913582.4	07-Sep-1990		
02854-016WO1	International	PCT	Expired	PCT/US90/05062	07-Sep-1990		
BONE REGENERATION							
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02854-026JP1	Japan	PCT	Abandoned	~~Hei-05-510253~~	~~26-May-1994~~		
02854-026EP1	Europe	PCT	Abandoned	93900683.9	24-Nov-1992		
02854-026WO1	International	PCT	Expired	PCT/US92/10214	24-Nov-1992		
MEDICAMENT FOR PROMOTING GROWTH OF MAMMALIAN NERVE - IMB Only							
02854-027AU1	Australia	PCT	Granted	30668/92	04-Nov-1992	673659	12-Mar-1997
02854-027CA1	Canada	PCT	Granted	2,123,685	04-Nov-1992	2,123,685	07-Oct-2003
02854-027CH1	Switzerland	PCT	Granted	2309/93-2	04-Nov-1992	684573	31-Oct-1994
02854-027JP1	Japan	PCT	Allowed	5-510115	04-Nov-1992		
02854-027JP2	Japan	PCT	Pending	2005-292267	28-Sep-2005		
02854-027EP1	Europe	PCT	Abandoned	92924312.9	04-Nov-1992		
02854-027PL1	Poland	PCT	Abandoned	P303981	04-Nov-1992		
02854-027ZA1	South Africa	PCT	Abandoned		04-Nov-1992		
02854-027WO1	International	PCT	Expired	PCT/US92/09545	04-Nov-1992		

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C & E Ref. No.	Country	Type	Status	Application No.	Filed	Patent No.	Issued
A DEVICE TO PROMOTE DRUG-INDUCED NERVE REGENERATION							
02854-033WO1	International	PCT	Expired	PCT/US95/00985	25-Jan-1995		
PYRIDINOLINE CROSSLINKS AS MARKERS OF PERIODONTAL AND PERI-IMPLANT DISEASE ACTIVITY							
02854-034AT1	Austria	EPC	Granted	95909234.7	13-Jan-1995	E220458	10-Jul-2002
02854-034BE1	Belgium	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034CA1	**Canada**	**PCT**	**Pending**	**2,183,452**	**13-Jan-1995**		
02854-034CH1	Switzerland	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034DE1	Germany	EPC	Granted	95909234.7	13-Jan-1995	69527350.7	10-Jul-2002
02854-034DK1	Denmark	PCT	Granted	95909234.7	13-Jan-1995	0745221	07-Oct-2002
02854-034EP1	Europe	PCT	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034ES1	Spain	EPC	Granted	95909234.7	13-Jan-1995	ES2179867T3	10-Jul-2002
02854-034FR1	France	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034GB1	Great Britain	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034GR1	Greece	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034IE1	Ireland	PCT	Granted	95909234.7	13-Jan-1995	0745221	
02854-034IT1	Italy	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034JP1	Japan	PCT	Granted	7-521795	13-Jan-1995	3,521,913	20-Feb-2004
02854-034KP1	N. Korea	PCT	Granted	96-0594	16-Aug-1996	31,331	22-Jan-1998
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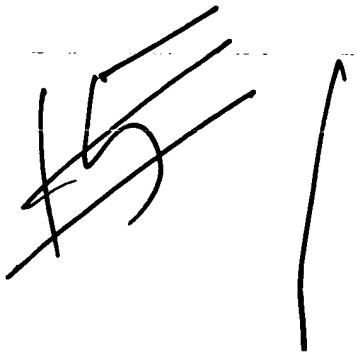
02854-034PT1	Portugal	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034PT1	Sweden	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034CN1	China	PCT	Abandoned	95192443.5	13-Jan-1995		
02854-034KR1	S. Korea	PCT	Abandoned	1996-704491	16-Aug-1996		
02854-034WO1	International	PCT	Expired	PCT/US95/00509	13-Jan-1995		



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United States Patent [19]

Antoniades et al.

[11] Patent Number: 5,124,316

[45] Date of Patent: Jun. 23, 1992

[54] METHOD FOR PERIODONTAL REGENERATION

[75] Inventors: Harry N. Antoniades, Newton; Samuel E. Lynch, Jamaica Plain, both of Mass.

[73] Assignees: President and Fellows of Harvard College, Cambridge; Institute of Molecular Biology, Inc., Boston, both of Mass.

[21] Appl. No.: 582,332

[22] Filed: Sep. 13, 1990

Related U.S. Application Data

[63] Continuation of Ser. No. 299,763, Jan. 23, 1989, abandoned, which is a continuation-in-part of Ser. No. 234,196, Aug. 18, 1988, abandoned, which is a continuation-in-part of Ser. No. 120,606, Nov. 16, 1987, abandoned, which is a continuation-in-part of Ser. No. 930,762, Nov. 14, 1986, abandoned.

[51] Int. Cl.[5] A61K 37/02; A61K 7/16

[52] U.S. Cl. 514/12; 514/21; 514/2; 424/49; 604/54; 604/46; 604/77

[58] Field of Search 514/2, 3, 21, 12; 424/101, 49; 604/54, 46, 77

[56] References Cited

U.S. PATENT DOCUMENTS

4,702,734 10/1987 Terranova 604/54

FOREIGN PATENT DOCUMENTS

0312208 4/1989 European Pat. Off. .

Primary Examiner—F. T. Moezie
Attorney, Agent, or Firm—Fish & Richardson

[57] ABSTRACT

A method for promoting bone, periodontium or ligament growth of a mammal comprising applying to the bone periodontium or ligament a growth-promoting amount of a composition comprising a partially purified or purified polypeptide growth factor.

1 Claim, 1 Drawing Sheet

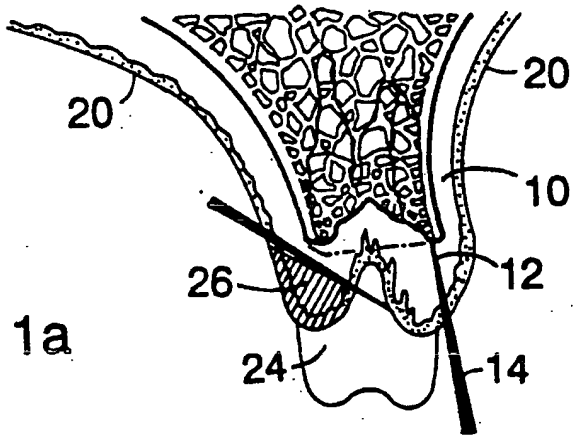


FIG. 1a

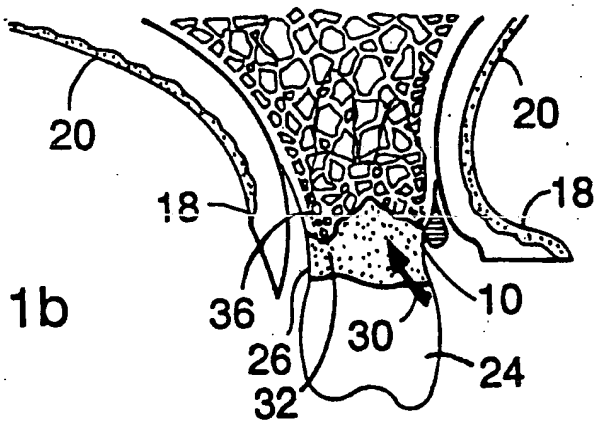


FIG. 1b

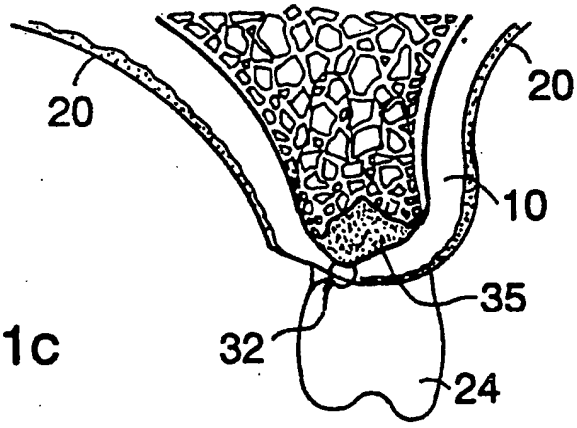


FIG. 1c

METHOD FOR PERIODONTAL REGENERATION

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Ser. No. 299,763, filed Jan. 23, 1989, which is a continuation-in-part of Antoniades et al., entitled "Wound Healing", U.S. Ser. No. 234,196, filed Aug. 18, 1988, which is a continuation-in-part of Antoniades et al., entitled "Wound Healing", U.S. Ser. No. 120,606, filed Nov. 16, 1987, which is a continuation-in-part of Antoniades et al., entitled "Healing External Wounds," U.S. Ser. No. 930,762, filed Nov. 14, 1986, all of which have been abandoned.

BACKGROUND OF THE INVENTION

This invention relates to the healing of bone and connective tissues.

Growth factors are polypeptide hormones which stimulate a defined population of target cells. Examples of growth factors include platelet-derived growth factor (PDGF), insulin-like growth factors (IGF-I and II), transforming growth factor beta (TGF-β), epidermal growth factor (EGF), and fibroblast growth factor (FGF). PDGF is a cationic, heat-soluble protein found in the granules of circulating platelets which is known to stimulate in vitro protein synthesis and collagen production by fibroblasts. It is also known to act as an in vitro mitogen and chemotactic agent for fibroblasts, smooth muscle cells, and glial cells.

It has been proposed to use PDGF to promote in vivo soft tissue wound healing. For example, Grotendorst (1984) J. Trauma 24:549–52 describes adding PDGF to Hunt-Schilling wire mesh chambers impregnated with a collagen gel and implanted in the backs of rats; PDGF was found to increase the amount of new collagen synthesized. However, Leitzel et al., (1985) J. Dermatol. Surg. Oncol. 11:617–22 were unable to accelerate normal wound healing in hamsters using PDGF alone or in combination with FGF and EGF.

Michaeli, et al. (1984) In *Soft and Hard Tissue Repair* (Hunt, T.K. et al., Eds), Praeger Publishers, New York, pp. 380–394, report that application of a partially purified preparation of PDGF obtained from platelet-rich plasma stimulated angiogenesis when implanted in rabbit corneas. Because PDGF is not an angiogenic growth factor the investigators suggested that an unknown factor in their partially purified PDGF preparation was responsible for the angiogenic effect.

Canalis (1985) Clin. Orthoped. Rel. Res. 193: 246–263 reports that PDGF stimulates DNA synthesis and nonspecific protein synthesis in calvariae in organ culture. In contrast, Tashijian, et al. (1982), Endocrinology 111:118 report that PDGF is a potent inducer of bone resorption in mouse calveria cultures. PDGF-stimulated bone resorption was mediated through increased prostaglandin production.

SUMMARY OF THE INVENTION

In a first aspect, the invention features a method for promoting bone, periodontium or ligament growth of a mammal. The method includes applying to the bone, periodontium or ligament a growth-promoting amount of a composition containing a partially purified or purified polypeptide growth factor.

In a related aspect, the invention features promoting periodontium or ligament growth of a mammal by applying to the periodontium or ligament a growth-promoting amount of a composition containing a partially purified or purified polypeptide growth factor or a partially purified or purified differentiation factor.

By polypeptide growth factor is meant a polypeptide, including a chain of at least 6 amino acids, which modulates the growth of one or more defined populations of target cells. By differentiation factor is meant a polypeptide, including a chain of at least 6 amino acids, which stimulates differentiation of one or more defined populations of target cells into cells with cartlidge or bone forming potential.

By promoting growth is meant to include healing of a wounded bone, periodontium or ligament, and regeneration of such tissues and structures. By promoting periodontium growth is meant to include regeneration or healing of the supporting tissues of a tooth including alveolar bone, cementum and interposed periodontal ligament, which have been damaged by disease or trauma.

In preferred embodiments, the step of applying includes applying a combination of a polypeptide growth factor and a differentiation factor; the polypeptide growth factor is chosen from platelet-derived growth factor, insulin-like growth factor I or insulin-like growth factor II, transforming growth factor β1, transforming growth factor β2, and transforming growth factor α; the differentiation factor is chosen from a bone morphogenetic protein (BMP) and osteogenin; most preferably the polypeptide growth factor is purified PDGF and the differentiation factor is partially purified or purified bone morphogenetic protein; the periodontium includes bone, cementum, and periodontal ligament; and the periodontium, bone, or ligament is damaged by disease or trauma, and the method includes applying to the mammal a disease-healing amount of the growth or differentiation factor.

In a related aspect, the invention features a method for preparing a composition for promoting growth of bone, periodontium or ligament. The method includes the step of mixing partially purified or purified platelet-derived growth factor in a pharmaceutically acceptable carrier substance.

In preferred embodiments, the pharmaceutically acceptable carrier substance is a natural or synthetic polymer, a bone substituting agent, or a viscous liquid or gel; most preferably the platelet derived growth factor is purified.

The compositions of this invention aid in regeneration of periodontium, at least in part, by promoting the growth of connective tissue, bone, and cementum, and by stimulating protein and collagen synthesis. Regeneration using a composition of this invention is a more effective treatment of periodontal diseases or bone wounds than that achieved using systemic antibiotics or surgical debridement alone.

In most preferred embodiments of the invention, the composition is prepared by combining partially purified or purified PDGF with a pharmaceutically acceptable carrier substance, e.g., natural and synthetic polymers (e.g., collagen, polyglycolic acid and polylactic acid), or bone substituting agents (e.g., tricalcium phosphate, hydroxyapatite, polymethylmethacrylate or demineralized freeze-dried cortical bone) or commercially available inert gels or liquids (e.g., methyl cellulose). In another most preferred embodiment, the invention features providing a composition including a combination

of purified PDGF and purified BMP in a pharmaceutically acceptable carrier substance.

The factors may be obtained from human tissues or cells, e.g., platelets, or by solid phase peptide synthesis, or by recombinant DNA technology. Thus, by the term "polypeptide growth factor" or "differentiation factor", we mean tissue or cell-derived, recombinant, and synthesized materials. If the factor is a dimer, e.g., PDGF, the recombinant factor can be a recombinant heterodimer, made by inserting into cultured prokaryotic or eukaryotic cells DNA sequences encoding both subunits of the factor, and then allowing the translated subunits to be processed by the cells to form a heterodimer. Alternatively, DNA encoding just one of the subunits (e.g., for PDGF preferably the beta or "2" chain) can be inserted into cells, which then are cultured to produce homodimeric factor (e.g., PDGF-1 or PDGF-2 homodimer).

The term "purified" as used herein refers to a growth or differentiation factor, e.g., PDGF, which, prior to mixing with a carrier substance, is 95% or greater by weight, i.e., the factor is substantially free of other proteins, lipids, and carbohydrates with which it is naturally associated. The term "partially purified" refers to a lesser purity of factor, having, for example, only 5%–95% by weight of the factor, preferably 65–95%.

A purified protein preparation will generally yield a single major band on a polyacrylamide gel. Most preferably, the purified factor used in compositions of the invention is pure as judged amino-terminal amino acid sequence analysis.

The composition of the invention provides a fast, effective method for healing bony wounds of mammals, e.g., fractures, implant recipient sites, and sites of periodontal disease. The composition enhances connective tissue and bone formation compared to natural healing (i.e., no exogenous agents added) or healing supplemented by addition of systemic antibiotics. Unlike natural healing, conventional surgical therapy, or antibiotics, the composition of the above factors in a carrier prompts increased bone, connective tissue, and cementum formation when applied to periodontal disease affected sites. The restoration of these tissues leads to an improved prognosis for the affected teeth. The ability of these factors to stimulate new bone formation also makes it applicable for treating bony defects caused by other types of infection or surgical or accidental trauma.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The drawings will first briefly be described.

DRAWINGS

FIG. 1 is a diagrammatic representation of a surgical procedure for periodontium regeneration.

Specifically, FIG. 1A shows an area of bone around a maxillary tooth which has been depleted by periodontal disease. Bone height in the absence of disease is shown by the dashed line. The arrows show surgical incision and reflection of gingival tissue.

FIG. 1B shows reflection of gingival tissue to expose a tooth root surface (covered by a mineralized layer of cementum) and bone. The root surface is cleaned by root planing. The arrow indicates the approximate area where a growth and/or differentiation factor is added in a pharmaceutically acceptable carrier substance to enhance regeneration or growth of bone, cementum and the interposed periodontal ligament.

FIG. 1C, shows suturing of gingival tissue. The shaded area indicates the position of placement of a growth and/or differentiation factor.

We now describe a preferred embodiment of the invention. Below is presented an example of use of PDGF as a bone and periodontum healing agent. As described above this example is not limiting to the invention, and those skilled in the art will recognize that the invention is broadly applicable as described in the Summary of the Invention and the claims.

EXAMPLE: PDGF

Osseous wounds, e.g., following periodontal disease or trauma, are treated, and peroidontium including bone, cementum, and connective tissue regenerated, according to the invention, with PDGF prepared by combining purified PDGF with any of the pharmaceutically acceptable carrier substances described above. Purified recombinant PDGF and purified PDGF derived from human platelets are commercially available from PDGF, Inc. (Boston, Mass.), Collaborative Research (Waltham, Mass.), and Amgen Corp. (Thousand Oaks, Calif.). Partially purified and purified PDGF can also be prepared as follows:

Five hundred to 1000 units of washed human platelet pellets are suspended in 1M NaCl (2 ml per platelet unit) and heated at 100° C. for 15 minutes. The supernatant is then separated by centrifugation and the precipitate extracted twice with the 1M NaCl.

The extracts are combined and dialyzed against 0.08M NaCl–0.01M sodium phosphate buffer (pH 7.4) and mixed overnight at 4° C. with CM-Sephadex C-50 equilibrated with the buffer. The mixture is then poured into a column (5×100 cm), washed extensively with 0.08M NaCl-0.01M sodium phosphate buffer (pH 7.4), and eluted with 1M NaCl while 10 ml fractions are collected.

Active fractions are pooled and dialyzed against 0.3M NaCl-0.01M sodium phosphate buffer (pH 7.4), centrifuged, and passed at 4° C. through a 2.5×25 cm column of Blue Sepharose (Pharmacia) equilibrated with 0.3M NaCl-0.01M sodium phosphate buffer (pH 7.4). The column is then washed with the buffer and partially purified PDGF eluted with a 1:1 solution of 1M NaCl and ethylene glycol.

The partially purified PDGF fractions are diluted (1:1) with 1M NaCl, dialyzed against 1M acetic acid, and lyophilized. The lyophilized samples are dissolved in 0.8M NaCl-0.01M sodium phosphate buffer (pH 7.4) and passed through a 1.2×40 cm column of CM-Sephadex C-50 equilibrated with the buffer. PDGF is then eluted with a NaCl gradient (0.08 to 1M).

The active fractions are combined, dialyzed against 1M acetic acid, lyophilized, and dissolved in a small volume of 1M acetic acid. 0.5 ml portions are applied to a 1.2×100 cm column of Biogel P-150 (100 to 200 mesh) equilibrated with 1M acetic acid. The PDGF is then eluted with 1M acetic acid while 2 ml fractions are collected.

Each active fraction containing 100 to 200 mg of protein is lyophilized, dissolved in 100 ml of 0.4% trifluoroacetic acid, and subjected to reverse phase high performance liquid chromatography on a phenyl Bon-

dapak column (Waters). Elution with a linear acetonitrile gradient (0 to 60%) yields pure PDGF.

PDGF made by recombinant DNA technology can be prepared as follows:

Platelet-derived growth factor (PDGF) derived from human platelets contains two polypeptide sequences (PDGF-1 and PDGF-2 polypeptides; Antoniades, H.N. and Hunkapiller, M. (1983) Science 220:963-965). PDGF-1 is encoded by a gene localized in chromosome 7 (Betsholtz, C. et al., Nature 320:695-699), and PDGF-2 is encoded by the sis oncogene (Doolittle, R. et al. (1983) Science 221:275-277) localized in chromosome 22 (Dalla-Favera, R. (1982) Science 218:686-688). The sis gene encodes the transforming protein of the Simian Sarcoma Virus (SSV) which is closely related to PDGF-2 polypeptide. The human cellular c-sis also encodes the PDGF-2 chain (Rao, C.D. et al. (1986) Proc. Natl. Acad. Sci. USA 83:2392-2396). Because the two polypeptide chains of PDGF are coded by two different genes localized in separate chromosomes, the possibility exists that human PDGF consists of a disulfide-linked heterodimer of PDGF-1 and PDGF-2, or a mixture of the two homodimers (homodimer of PDGF-1 and homodimer of PDGF-2), or a mixture of the heterodimer and the two homodimers.

Mammalian cells in culture infected with the Simian Sarcoma Virus, which contains the gene encoding the PDGF-2 chain, were shown to synthesize the PDGF-2 polypeptide and to process it into a disulfide-linked homodimer (Robbins et al. (1983) Nature 305:605-608). In addition, PDGF-2 homodimer reacts with antisera raised against human PDGF. Furthermore, the functional properties of the secreted PDGF-2 homodimer are similar to those of platelet-derived PDGF in that it stimulates DNA synthesis in cultured fibroblasts, it induces phosphorylation at the tyrosino residue of a 185 kd cell membrane protein, and it is capable of competing with human (^{125}I)-PDGF for binding to specific cell surface PDGF receptors (Owen, A. et al. (1984) Science 225:54-56). Similar properties were shown for the sis/PDGF-2 gene product derived from cultured normal human cells (for example, human arterial endothelial cells), or from human malignant cells expressing the sis/PDGF-2 gene (Antoniades, H. et al. (1985) Cancer Cells 3:145-151).

The recombinant PDGF-2 homodimer is obtained by the introduction of cDNA clones of c-sis/PDGF-2 gene into mouse cells using an expression vector. The c-sis/PDGF-2 clone used for the expression was obtained from normal human cultured endothelial cells (Collins, T., et al. (1985) Nature 216:748-750).

PERIODONTAL AND BONE REGENERATION

To determine the effectiveness of PDGF in promoting periodontium and bone growth, the following experiments were performed.

Six year old beagle dogs (Laboratory Research Enterprises, Kalamazoo, Mich.) with naturally occurring periodontal disease were selected on the basis of an initial radiographic examination of their teeth. Teeth which exhibited 20% to 80% reduction of surrounding jaw bone were initially scaled using ultrasonic instruments. Referring to FIG. 1, an example of such reduction is shown, where a diseased jaw bone 10 (the extent of a normal bone is shown by dashed line 12) exhibits about 20% reduction in size due to the disease. A conventional gingival full thickness surgical flap 18 is then produced by an incision, shown at arrow 14, and 16. This removes gingiva 20 from around jaw bone 10 and tooth 24. Root 26 of the tooth is then planed to remove bacterial plaque and calculus. The experimental teeth were treated by the topical application of 500 ng to 5 mg, but generally one microgram of purified PDGF per tooth in a pharmacuetically acceptable carrier substance, e.g., a commercially available inert gel such as methyl cellulose, as shown by arrow 30. Generally, the PDGF is applied to the root of the tooth at the point where the cementum has been planed. It is thus near or adjacent cementum 32, bone 10, and interposed periodontal ligament (not shown). The remaining teeth received the carrier alone. The gingival flap was then placed back to near its original position and held together by a suture 32. The position of the PDGF-containing methyl cellulose is shown by shaded area 35.

Block biopsies of the teeth and surrounding bone were taken at two weeks post-treatment and prepared for histologic evaluation using standard demineralizing (10% trifluoroacetic acid) and processing techniques. Sections were stained with hematoxylin and eosin to allow old and new bone cementum and periodontal ligament to be differentiated.

RESULTS

Results of histologic analyses of periodontal and bone specimens indicated that, in PDGF-treated specimens: a) new bone was formed adjacent the root surfaces, b) a deposit resembling cementum was formed on the root surface adjacent the new bone, c) new bone was also formed on the periosteal and endosteal surfaces of the specimens, —d) evidence of ankylosis (fusion of bone and root surfaces) due to bone growth was present within the apical extent of the periodontal ligament, e) a dense layer of osteoblasts lined the newly formed bone, f) some osteoblasts were incorporated into the forming bone and formed osteocytes, g) a dense band of osteoblast-like cells was present within the connective tissue immediately coronal to the area of newly forming bone, and h) newly formed collagen fibers were observed inserting into the newly formed cementum deposits on the root surface. Thus, in treated sites, periodontal regeneration was occurring, including reformation of bone, connective tissue (periodontal ligament), and cementum.

In the control specimens there was no evidence of new bone formation, and there was an absence of new cementum-like deposits. Gingival connective tissue immediately coronal to the alveolar bone was oriented perpendicular to the bony surface appearing to form a "cap" over the original bone. There was no sign of any periodontal regeneration occurring. This is the first time that a purified polypeptide growth or differentiation factor, such as PDGF, has been demonstrated to enhance periodontal regeneration. These results indicate that the composition of the invention enhances osteogenic, cementogenic, and connective tissue responses.

USE

PDGF alone or in combination with other growth factors is useful for promoting bone healing, bone growth and regeneration or healing of the supporting structures of teeth injured by trauma or disease. It is also useful for promoting healing of a site of extraction of a tooth, for mandibular ridge augmentation, or at tooth implant sites. Bone healing would also be enhanced at sites of bone fracture or in infected areas, e.g., osteomy-

elitis, or at tumor sites. PDGF is also useful for promoting growth and healing of a ligament, e.g., the periodontal ligament, and of cementum.

In use, the PDGF or other growth or differentiation factor is applied directly to the area needing healing or regeneration. Generally, it is applied in a resorbable or non-resorbable carrier as a liquid or solid, and the site then covered with a bandage or nearby tissue. An amount sufficient to promote bone growth is generally between 500 ng and 5 mg for a 1 cm^2 area, but the upper limit is really one of for a 1 cm^2 area, but the upper limit is really one of expense of the PDGF, and is not a physiological limit.

Other embodiments are within the following claims.

We claim:

1. A method of promoting growth of damaged bone, periodontium, or ligament of a living mammal, comprising the steps of

producing a surgical flap of skin to expose said damaged bone, periodontium, or ligament,

planing said damaged bone or periodontium to remove organic matter from said bone or periodontium

applying platelet derived growth factor in a pharmaceutically acceptable carrier to said exposed bone, periodontium, or ligament,

replacing said flap, and

allowing said damaged bone, periodontium, or ligament to regrow.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,124,316

DATED : June 23, 1992

INVENTOR(S) : Harry N. Antoniades, et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1, line 26, change "heat-soluble protein" to --heat-stable protein--;

Column 2, line 11, correct the spelling of "cartilage";

Column 7, lines 11-12, delete the following: --for a 1 cm^2 area, but the upper limit is really one of--.

Signed and Sealed this

Sixteenth Day of November, 1993

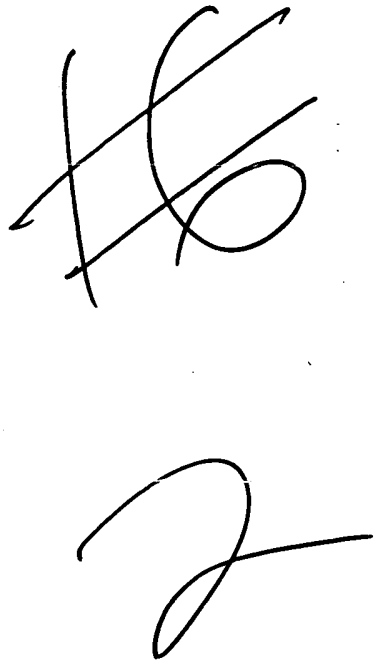
Bruce Lehman

BRUCE LEHMAN

Commissioner of Patents and Trademarks

Attest:

Attesting Officer



UNITED STATES PATENT AND TRADEMARK OFFICE

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Customer Num: 21559

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON MA 02110

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the U.S. Patent and Trademark Office. If the maintenance fee and any necessary surcharge have been timely paid for the patent listed below, the notation "PAID" will appear in the "STAT" column.

If the statement of small entity status is defective the reason will be indicated below in the "Small Entity" status column. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

PATENT NUMBER	FEE AMT	SUR CHARGE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	STAT	ATTY DKT NUMBER
5,124,316	$495.00	$0.00	07/582,332	06/23/92	09/13/90	04	NO	PAID	02854/015002

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UNITED STATES PATENT AND TRADEMARK OFFICE

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PATENT NUMBER	FEE AMT	SUR CHARGE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	STAT	ATTY DKT NUMBER
5,124,316	$1,900.00	$0.00	07/582,332	06/23/92	09/13/90	08	NO	PAID	02854/015002

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The data shown below is from the records of the U.S. Patent and Trademark Office. If the maintenance fee and any necessary surcharge have been timely paid for the patent listed below, the notation "PAID" will appear in the "STAT" column.

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PATENT NUMBER	FEE AMT	SUR CHARGE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	STAT	ATTY DKT NUMBER
5,124,316	$3,220.00	$0.00	07/582,332	06/23/92	09/13/90	12	NO	PAID	02854/015002

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3

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,124,316

DATED : June 23, 1992

INVENTOR(S) : Harry N. Antoniades, et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1, line 26, change "heat-soluble protein" to --heat-stable protein--;

Column 2, line 11, correct the spelling of "cartilage";

Column 7, lines 11-12, delete the following: --for a 1 cm^2 area, but the upper limit is really one of--.

Signed and Sealed this

Sixteenth Day of November, 1993

Attest:

Mary L. Adams

Attesting Officer

Bruce Lehman

BRUCE LEHMAN

Commissioner of Patents and Trademarks

4

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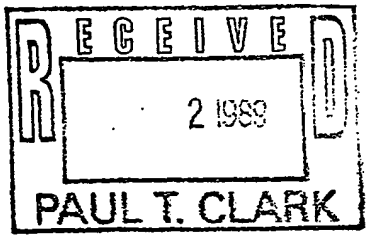
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231



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BOSTON, MA 02111-2658

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ASSIGNOR: 001 LYNCH, SAMUEL E. DOC DATE: 02/17/89

RECORDATION DATE: 02/27/89 NUMBER OF PAGES 001 REEL/FRAME 5027/0089

DIGEST: ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE: 501 PRESIDENT AND FELLOWS OF HARVARD COLLEGE, THE, CAMBRIDGE, MA., A MA. CORP.

SERIAL NUMBER 7-299763 FILING DATE 01/23/89
PATENT NUMBER ISSUE DATE 00/00/00

TITLE OF INVENTION: WOUND HEALING

INVENTOR: 001 ANTONIADES, HARRY N.
INVENTOR: 002 LYNCH, SAMUEL E.

ASSIGNMENT

For valuable consideration, I, Samuel (FIRST) E. (MIDDLE INITIAL) Lynch (LAST)

of Jamaica Plain (CITY OR TOWN), Massachusetts (STATE) hereby assign

to THE PRESIDENT AND FELLOWS OF HARVARD COLLEGE, a

Massachusetts corporation having a place of business

at Cambridge, Massachusetts,

and its successors and assigns (collectively hereinafter called "the Assignee"), the entire right, title and interest throughout the world in the inventions and improvements which are the subject of an application for United States Serial No. 299,763 filed January 20, 1989, entitled WOUND HEALING

this assignment including said application, any and all United States and foreign patents granted for any of said inventions or improvements, and the right to claim priority based on the filing date of said application under the International Convention for the Protection of Industrial Property, the Patent Cooperation Treaty, the European Patent Convention, and all other treaties of like purposes; and I authorize the Assignee to apply in all countries in my name or in its own name for patents and like rights of exclusion and for inventor's certificates for said inventions and improvements; and I agree for myself and my heirs, legal representatives and assigns, without further compensation to perform such lawful acts and to sign such further applications, assignments, Preliminary Statements and other lawful documents as the Assignee may reasonably request to effectuate fully this assignment.

In Witness Whereof, I hereto set my hand and seal at Boston, Massachusetts, this 17 day of February, 1989.

/s/ Samuel E. Lynch L.S.

(FIRST) Samuel (MIDDLE INITIAL) E. (LAST) Lynch

State of Massachusetts :
ss.
County of Suffolk :

Before me this 17 day of February, 19 89, personally appeared Samuel E. Lynch known to me to be the person whose name is subscribed to the foregoing Assignment and acknowledged that he executed the same as his free act and deed for the purposes therein contained.

/s/ Deborah A. McKenzie
Notary Public

[Notary's seal here]

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FEB 27 89

My commission expires: Nov. 16, 1995

/s/ [illegible]
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ASSIGNOR: 001 ANTONIADES, HARRY N. DOC DATE: 02/17/89

RECORDATION DATE: 02/27/89 NUMBER OF PAGES 001 REEL/FRAME 5027/0090

DIGEST: ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE: 501 INSTITUTE OF MOLECULAR BIOLOGY, THE, BOSTON, MA., A DE. CORP.

SERIAL NUMBER 7-299763 FILING DATE 01/23/89
PATENT NUMBER ISSUE DATE 00/00/00

TITLE OF INVENTION: WOUND HEALING

INVENTOR: 001 ANTONIADES, HARRY N.
INVENTOR: 002 LYNCH, SAMUEL E.

ASSIGNMENT

For valuable consideration, I, Harry (FIRST) N. (MIDDLE INITIAL) Antoniades (LAST)

of Newton (CITY OR TOWN), Massachusetts (STATE) hereby assign

to THE INSTITUTE OF MOLECULAR BIOLOGY, Inc., a

Delaware corporation having a place of business

at Boston, Massachusetts,

and its successors and assigns (collectively hereinafter called "the Assignee"), the entire right, title and interest throughout the world in the inventions and improvements which are the subject of an application for United States ~~Patent~~ Serial No. 299,763 filed January 20, 1989 ~~this day~~, entitled WOUND HEALING

this assignment including said application, any and all United States and foreign patents granted for any of said inventions or improvements, and the right to claim priority based on the filing date of said application under the International Convention for the Protection of Industrial Property, the Patent Cooperation Treaty, the European Patent Convention, and all other treaties of like purposes; and I authorize the Assignee to apply in all countries in my name or in its own name for patents and like rights of exclusion and for inventor's certificates for said inventions and improvements; and I agree for myself and my heirs, legal representatives and assigns, without further compensation to perform such lawful acts and to sign such further applications, assignments, Preliminary Statements and other lawful documents as the Assignee may reasonably request to effectuate fully this assignment.

In Witness Whereof, I hereto set my hand and seal at Boston, Massachusetts, this 17 day of February, 1989.

Harry N. Antoniades L.S.
(FIRST) Harry (MIDDLE INITIAL) N. (LAST) Antoniades

State of Massachusetts :
ss.
County of Suffolk :

Before me this 17 day of February, 19 89, personally appeared Harry N. Antoniades known to me to be the person whose name is subscribed to the foregoing Assignment and acknowledged that he executed the same as his free act and deed for the purposes therein contained.

Deborah G. McIntyre
Notary Public

[Notary's seal here]

My commission expires: Nov 16, 1995

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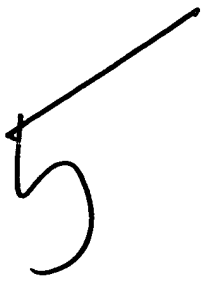

ASSIGNMENT

For valuable consideration, we,

Full Name of Assignor	City	State (and Country if not USA)
Institute of Molecular Biology, Inc.	Delaware	P.O. Box 4278 Shrewsbury, MA 01545

hereby assign to

Full Name of Assignee	State of Incorporation	Business Address
BioMimetic Therapeutics, Inc.	Delaware	389 Nichol Mill Lane Franklin, TN 37067

and to its successors and assigns (collectively hereinafter called "the Assignee"), the entire right, title, and interest throughout the world in the inventions and improvements which are the subject of one or more of the patents and applications listed on Schedule A, which is attached hereto.

This assignment includes the patents and applications listed in the attached Schedule A, any and all United States and foreign patents, utility models, and design registrations granted for any of said inventions or improvements, and the right to claim priority based on the filing date of any of the patents and applications listed in the attached Schedule A under the International Convention for the Protection of Industrial Property, the Patent Cooperation Treaty, the European Patent Convention, and all other treaties of like purposes; and we authorize the Assignee to apply in all countries in our names or in its own name for patents, utility models, design registrations, and like rights of exclusion, and for inventors' certificates for said inventions and improvements; and we agree for ourselves and our respective heirs, legal representatives and assigns, without further compensation, to perform such lawful acts and to sign such further applications, assignments, Preliminary Statements, and other lawful documents as the Assignee may reasonably request to effectuate fully this assignment.

IN WITNESS WHEREOF, I hereto set my hand and seal at SHREWSBURY, MASSACHUSETTS,
this 4th day of November, 2005

John M. Naples L.S.

John M. Naples, President
Institute of Molecular Biology, Inc.

STATE OF MASSACHUSETTS :

:ss.

COUNTY OF WORCESTER :

Before me this 4th day of November, 2005, before me, the undersigned notary public, personally appeared John M. Naples, proved to me through satisfactory evidence of identification, which consisted of MASSACHUSETTS DRIVERS LICENSE, to be the person whose name is subscribed to the foregoing Assignment, and acknowledged that he executed the same as his free act and deed for the purposes therein contained.

Notary Public

My Commission Expires: 020708

[Notary's Seal Here]

PATRICIA MACISAAC
Notary Public
Commonwealth of Massachusetts
My Commission Expires
February 7, 2008

Schedule A
(Page 1 of 5)

C&E Ref/Nos	Status	Title	Application Nos	Filed	Patent Nos	Dated
02854-007001	Abandoned	WOUND HEALING AND BONE REGENERATION	06/930,762	14-Nov-1986		
02854-009001	Issued	WOUND HEALING AND BONE REGENERATION USING PDGF AND IGF-1	07/120,943	16-Nov-1987	4,861,757	29-Aug-1989
02854-010001	Issued	WOUND HEALING COMPOSITION OF TGF-ALPHA AND PDGF	07/136,399	22-Dec-1987	4,874,746	17-Oct-1989
02854-011001	Issued	WOUND HEALING USING IGF-I AND TGFβ	07/196,975	20-May-1988	4,983,581	8-Jan-1991
02854-011002	Abandoned	WOUND HEALING USING IGF-I AND TGFβ	07/530,649	30-May-1990		
02854-011003	Issued	WOUND HEALING USING IGF-II AND TGF	07/857,713	25-Mar-1992	5,256,644	26-Oct-1993
02854-012001	Issued	PROCESS OF WOUND HEALING USING PDGF AND EGF	07/231,145	10-Aug-1988	5,034,375	23-Jul-1991
02854-013003	Abandoned	WOUND HEALING	07/449,303	5-Dec-1989		
02854-013004	Abandoned	WOUND HEALING	07/639,060,303	9-Jan-1991		
02854-014001	Issued	WOUND HEALING USING PDGF AND IGF-II	07/272,090	16-Nov-1988	5,019,559	28-May-1991
02854-015001	Abandoned	WOUND HEALING	07/299,763	23-Jan-1989		
02854-015002	Issued	METHOD OF PERIDONTAL REGENERATION	07/582,332	13-Sep-1990	5,124,316	23-Jun-1992
02854-016001	Issued	WOUND HEALING COMPOSITION OF IL-1 AND PDGF OR IGF-1	07/403,969	7-Sep-1989	5,035,887	30-Jul-1991
02854-026001	Abandoned	BONE REGENERATION	07/799,375	27-Nov-1991		
02854-027001	Issued	NERVE REGENERATION	08/198,542	18-Feb-1994	6,506,727	14-Jan-2003
02854-033001	Issued	DEVICE TO PROMOTE DRUG-INDUCED NERVE REGENERATION	08/187,210	26-Jan-1994	5,656,605	12-Aug-1997
02854-034001	Issued	PYRIDINOLINE CROSSLINKS AS MARKERS OF PERIODONTAL AND PERI-IMPLANT DISEASE ACTIVITY	08/197,131	16-Feb-1994	5,516,699	14-May-1996

Schedule A
(Page 2 of 5)

C&E Ref. No.	Country	Type	Status	Application No.	Filed	Patent No(s).	Issued
WOUND HEALING AND BONE REGENERATION							
02854-007AT 1	Austria	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007AU1	Australia	PCT	Granted	83289/87	13-Nov-1987	600069	02-Aug-1990
02854-007BE1	Belgium	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007CA1	Canada	PCT	Granted	551,909	16-Nov-1987	1,322,714	05-Oct-1993
02854-007CH1	Switzerland	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007CN1	China	PCT	Granted	87101250.2	14-Nov-1987	87101250.2	30-Oct-1994
02854-007DE1	Germany	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007DK1	Denmark	PCT	Granted	3932/88	13-Nov-1987	25-Jul-81	30-May-05
02854-007EP1	Europe	PCT	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007FR1	France	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007FR2	France	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-007GB1	Great Britain	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007IE1	Ireland	PCT	Granted	3075/87	13-Nov-1987	60517	20-Jul-1994
02854-007IT1	Italy	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007JP1	Japan	PCT	Granted	500179/87	13-Nov-1987	1868245	26-Aug-1994
02854-007KR1	Korea	PCT	Granted	88-700829	13-Nov-1987	106260	17-Oct-1998
02854-007LU1	Luxembourg	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007NL1	Netherlands	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007NZ1	New Zealand	PCT	Granted	222551	16-Nov-1987	222551	
02854-007SE1	Sweden	EPC	Granted	87907900.2	13-Nov-1987	0289584	05-May-1993
02854-007TW1	Taiwan	PCT	Granted	76107672	15-Dec-1987	NI-51493	30-Jan-1992
02854-007ZA1	South Africa	PCT	Granted	87/8566	16-Nov-1987	87/8566	26-Jul-1989
02854-007OA1	Africa (OAPI)	PCT	Abandoned	PV59385	13-Nov-1987	9159	31-Mar-1992
02854-007MX1	Mexico	PCT	Abandoned	930672	16-Nov-1987	170454	23-Aug-1993
02854-007NO1	Norway	PCT	Abandoned	88/3127	13-Nov-1987		
02854-007WO1	International	PCT	Expired	PCT/US87/02975	13-Nov-1987		
WOUND HEALING							
02854-010AT1	Austria	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010AU1	Australia	PCT	Granted	37472/89	20-Dec-1988	613776	03-Dec-1991
02854-010BE1	Belgium	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010CA1	Canada	PCT	Granted	586,562	21-Dec-1988	1,322,164	14-Sep-1993
02854-010CH1	Switzerland	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010CN1	China	PCT	Granted	88109273.8	21-Dec-1988	88109273.8	19-Jul-1994
02854-010DE1	Germany	EPC	Granted	89901681.0	20-Dec-1988	P3885300.0	27-Oct-1993
02854-010DK1	Denmark	PCT	Granted	4122/89	20-Dec-1988	175947	08-Aug-2005
02854-010EP1	Europe	PCT	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010FR1	France	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010GB1	Great Britain	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010IE1	Ireland	PCT	Granted	3833/88	21-Dec-1988	61283	14-Oct-1994
02854-010IT1	Italy	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010JP1	Japan	PCT	Granted	501944/89	20-Dec-1988	1923551	25-Apr-1995
02854-010LU1	Luxembourg	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010MX1	Mexico	PCT	Granted	14307	22-Dec-1988	164966	09-Oct-1992
02854-010NL1	Netherlands	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010NZ1	New Zealand	PCT	Granted	227429	21-Dec-1988	227429	14-May-1991
02854-010SE1	Sweden	EPC	Granted	89901681.0	20-Dec-1988	0394349	27-Oct-1993
02854-010TW1	Taiwan	PCT	Granted	78100693	01-Feb-1989	NI-51930	20-Feb-1992
02854-010ZA1	South Africa	PCT	Granted	88/9594	22-Dec-1988	88/9594	27-Sep-1989
02854-010OA1	Africa (OAPI)	PCT	Abandoned	PV59630	20-Dec-1988	9129	31-Oct-1991
02854-010KR1	Korea	PCT	Abandoned	89/701555	20-Dec-1988		
02854-010NO1	Norway	PCT	Abandoned	89/3348	20-Dec-1988		
02854-010RU1	Russian Federation	PCT	Abandoned	4742130.14	20-Dec-1988		
02854-010WO1	International	PCT	Expired	PCT/US88/04557	20-Dec-1988		

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C & E Ref. No.	Country	Type	Status	Application No.	Filed	Patent No.	Issued
WOUND HEALING							
02854-011AT1	Austria	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011AT2	Austria	EPC	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011BE1	Belgium	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011BE2	Belgium	EPC	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011CA2	Canada	PCT	Granted	2,082,420	30-May-1991	2082420	20-Jul-2004
02854-011CH1	Switzerland	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011CH2	Switzerland	EPC	Granted	91910904.1	30-May-1991	531425	14-Aug-2002
02854-011DE1	Germany	EPC	Granted	89906917.3	22-May-1989	P68917300.8	03-Aug-1994
02854-011DE2	Germany	EPC	Granted	69133087.5	30-May-1991	0531425	14-Aug-2002
02854-011DK2	Denmark	EPC	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011EP1	Europe	PCT	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011EP2	Europe	PCT	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011ES2	Spain	EPC	Granted	0531425	30-May-1991	0531425	14-Aug-2002
02854-011FR1	France	EPC	Granted	0419534	22-May-1989	0419534	03-Aug-1994
02854-011FR2	France	EPC	Granted	0531425	30-May-1991	0531425	14-Aug-2002
02854-011GB1	Great Britain	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011GB2	Great Britain	EPC	Granted	0531425	30-May-1991	0531425	14-Aug-2002
02854-011GR2	Greece	EPC	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011IT1	Italy	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011IT2	Italy	EPC	Granted	0531425	30-May-1991	0531425	14-Aug-2002
02854-011JP1	Japan	PCT	Granted	506485/89	22-May-1989	1924479	25-Apr-1995
02854-011JP2	Japan	PCT	Granted	3-510861	30-May-1991	3,377,524	06-Dec-2002
02854-011LI2	Liechtenstein	EPC	Granted	91910904.1	30-May-1991	531425	14-Aug-2002
02854-011LU1	Luxembourg	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011LU2	Luxembourg	EPC	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011NL1	Netherlands	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011NL2	Netherlands	EPC	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011SE1	Sweden	EPC	Granted	89906917.3	22-May-1989	0419534	03-Aug-1994
02854-011SE2	Sweden	EPC	Granted	91910904.1	30-May-1991	0531425	14-Aug-2002
02854-011ES1	Spain	PCT	Abandoned	531425	30-May-1991		
02854-011WO1	International	PCT	Expired	PCT/US89/02229	22-May-1989		
02854-011WO2	International	PCT	Expired	PCT/US91/03829	30-May-1991		
WOUND HEALING							
02854-012AT1	Austria	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012BE1	Belgium	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012CA1	Canada	PCT	Granted	607,968	10-Aug-1989	1336816	29-Aug-1995
02854-012CH1	Switzerland	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012DE1	Denmark	EPC	Granted	89910545.6	10-Aug-1989	P68912758	26-Jan-1994
02854-012DE1	Germany	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012EP1	Europe	PCT	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012FR1	France	EPC	Granted	89910545.6	10-Aug-1989	382841	26-Jan-1994
02854-012GB1	Great Britain	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012IT1	Italy	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012JP1	Japan	PCT	Granted	509811/89	10-Aug-1989	1975393	27-Sep-1995
02854-012LU1	Luxembourg	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012NL1	Netherlands	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012SE1	Sweden	EPC	Granted	89910545.6	10-Aug-1989	0382841	26-Jan-1994
02854-012WO1	International	PCT	Expired	PCT/US89/03490	10-Aug-1989		

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C1&E Ref. No.	Country	Type	Status	Application No.	Filed	Patent No.	Issued
WOUND HEALING USING PDGF AND IGF-II							
02854-014AT1	Austria	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014BE1	Belgium	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014CA1	Canada	PCT	Granted	2,060,208	10-Apr-1990	2,060,208	20-Feb-2001
02854-014CH1	Switzerland	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014DE1	Germany	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014DK1	Denmark	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014EP1	Europe	PCT	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014ES1	Spain	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014FR1	France	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014GB1	Great Britain	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014IT1	Italy	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014JP1	Japan	PCT	Granted	507475/90	10-Apr-1990	2030420	19-Mar-1998
02854-014LU1	Luxembourg	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014NL1	Netherlands	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014SE1	Sweden	EPC	Granted	90907577.2	10-Apr-1990	0479799	06-Aug-1997
02854-014WO1	International	PCT	Expired	PCT/US90/01936	10-Apr-1990		
WOUND HEALING							
02854-016CA1	Canada	PCT	Pending	2,040,410	07-Sep-1990		
02854-016JP1	Japan	PCT	Granted	2-512565	07-Sep-1990	1969836	18-Sep-1995
02854-016EP1	Europe	PCT	Abandoned	90913582.4	07-Sep-1990		
02854-016WO1	International	PCT	Expired	PCT/US90/05062	07-Sep-1990		
BONE REGENERATION							
02854-026CA1	Canada	PCT	Abandoned	2,123,803	24-Nov-1992		
02854-026JP1	Japan	PCT	Abandoned	Hei-05-510253	25-May-1994		
02854-026EP1	Europe	PCT	Abandoned	93900683.9	24-Nov-1992		
02854-026WO1	International	PCT	Expired	PCT/US92/10214	24-Nov-1992		
MEDICAMENT FOR PROMOTING GROWTH OF MAMMALIAN NERVE - IMB Only							
02854-027AU1	Australia	PCT	Granted	30668/92	04-Nov-1992	673659	12-Mar-1997
02854-027CA1	Canada	PCT	Granted	2,123,685	04-Nov-1992	2,123,685	07-Oct-2003
02854-027CH1	Switzerland	PCT	Granted	2309/93-2	04-Nov-1992	684573	31-Oct-1994
02854-027JP1	Japan	PCT	Allowed	5-510115	04-Nov-1992		
02854-027JP2	Japan	PCT	Pending	2005-292267	28-Sep-2005		
02854-027EP1	Europe	PCT	Abandoned	92924312.9	04-Nov-1992		
02854-027PL1	Poland	PCT	Abandoned	P303981	04-Nov-1992		
02854-027ZA1	South Africa	PCT	Abandoned		04-Nov-1992		
02854-027WO1	International	PCT	Expired	PCT/US92/09545	04-Nov-1992		

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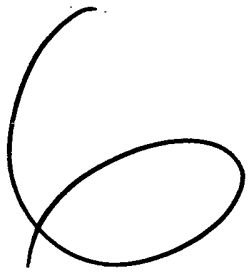
C&E Ref No	Country	Type	Status	Application No.	Filed	Patent No.	Issued
A DEVICE TO PROMOTE DRUG-INDUCED NERVE REGENERATION							
02854-033WO1	International	PCT	Expired	PCT/US95/00985	25-Jan-1995		
PYRIDINOLINE CROSSLINKS AS MARKERS OF PERIODONTAL AND PERI-IMPLANT DISEASE ACTIVITY							
02854-034AT1	Austria	EPC	Granted	95909234.7	13-Jan-1995	E220458	10-Jul-2002
02854-034BE1	Belgium	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034CA1	**Canada**	**PCT**	**Pending**	**2,183,452**	**13-Jan-1995**		
02854-034CH1	Switzerland	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034DE1	Germany	EPC	Granted	95909234.7	13-Jan-1995	69527350.7	10-Jul-2002
02854-034DK1	Denmark	PCT	Granted	95909234.7	13-Jan-1995	0745221	07-Oct-2002
02854-034EP1	Europe	PCT	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034ES1	Spain	EPC	Granted	95909234.7	13-Jan-1995	ES2179867T3	10-Jul-2002
02854-034FR1	France	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034GB1	Great Britain	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034GR1	Greece	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034IE1	Ireland	PCT	Granted	95909234.7	13-Jan-1995	0745221	
02854-034IT1	Italy	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034JP1	Japan	PCT	Granted	7-521795	13-Jan-1995	3,521,913	20-Feb-2004
02854-034KP1	N. Korea	PCT	Granted	96-0594	16-Aug-1996	31,331	22-Jan-1998
02854-034NL1	Netherlands	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034PT1	Portugal	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034PT1	Sweden	EPC	Granted	95909234.7	13-Jan-1995	0745221	10-Jul-2002
02854-034CN1	China	PCT	Abandoned	95192443.5	13-Jan-1995		
02854-034KR1	S. Korea	PCT	Abandoned	1996-704491	16-Aug-1996		
02854-034WO1	International	PCT	Expired	PCT/US95/00509	13-Jan-1995		



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Mr. Mark Citron
Vice President
Biomimetic Pharmaceuticals, Incorporated
389-A Nichol Mill Lane
Franklin, Tennessee 37067

NOV 18 2005

Re: P040013
GEM 21S (Growth-factor Enhanced Matrix)
Filed: March 14, 2004
Amended: March 25, April 9, 14, July 7,8,26,28, August 4, September 3,14,22, October 7,12,13,28, November 3, 2004 February 3,4,14,16, March 2,3,7,8,18,25, April 4,14,25, May 18, July 14,15, August 8,9, 18, 31, September 21, 26 and October 7, 2005.
Procode: NPZ

Dear Mr. Citron:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the GEM 21S (Growth-factor Enhanced Matrix). This device is indicated to treat the following periodontally related defects:

- Intrabony periodontal defects
- Furcation periodontal defects
- Gingival recession associated with periodontal defects.

We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions described below and in the "Conditions of Approval" (enclosed).

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that, to ensure the safe and effective use of the device, the device is further restricted within the meaning of section 520(e) under the authority of section 15(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

In addition to the postapproval requirements outlined in the enclosure, you have agreed to

- establish, and validate an immunological identity test for rhPDGF-BB received from the manufacturer. The information will be submitted as a supplement for FDA review by June 1, 2006. Following review and approval by the FDA, the new assay

will replace SDS-PAGE as an identity test for the incoming bulk drug substance.

- evaluate the historical release and stability specifications for GEM21S following manufacturing of 30 lots of product and submit the results as a report to the PMA with any proposed changes by September 1, 2006. Any proposal to broaden or shift the specifications should be submitted as a supplement to the premarket approval application.
- not use lots of PDGF drug substance for manufacture of GEM 21S which was fermented after September, 2002 until supplemental approval is received from FDA to include the PDGF fermentation site.

Expiration dating for this device has been established and approved at 18 months.

Please be aware that changing reference standards will change the potency specification, so a supplement must be submitted with each change to a reference standard. We suggest you send the details of the protocol for qualification and expiration dating of new reference standards to us for review before starting any of the testing.

CDRH does not evaluate information related to contract liability warranties, however you should be aware that any such warranty statements must be truthful, accurate, and not misleading, and must be consistent with applicable Federal and State laws.

CDRH will notify the public of its decision to approve your PMA by making available a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at http://www.fda.gov/cdrh/pmapage.html. Written requests for this information can also be made to the Dockets Management Branch, (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with any postapproval requirement constitutes a ground for withdrawal of approval of a PMA. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. The labeling will not routinely be reviewed by FDA staff when PMA applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form.

If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Ms. Angela Blackwell at (301) 827-5283.

Sincerely yours,

Donna-Bea Tillman Ph.D., M.P.A.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Last Modified: 1-31-02

CONDITIONS OF APPROVAL

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e) or (f). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations that require a PMA supplement cannot be briefly summarized; therefore, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report (see below). FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

Alternate submissions permitted under 21 CFR 814.39(f) for manufacturing process changes include the use of a 30-day Notice. The manufacturer may distribute the device 30 days after the date on which the FDA receives the 30-day Notice, unless the FDA notifies the applicant within 30 days from receipt of the notice that the notice is not adequate.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

1. Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

2. Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

   a. unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

   b. reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

1. A mix-up of the device or its labeling with another article.

2. Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and:

   a. has not been addressed by the device's labeling; or

   b. has been addressed by the device's labeling but is occurring with unexpected severity or frequency.

3. Any significant chemical, physical or other change or deterioration in the device, or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION.
The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984. This regulation was replaced by the reporting requirements of the Safe Medical Devices Act of 1990 which became effective July 31, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to the FDA whenever they receive or otherwise become aware of information, from any source, that reasonably suggests that a device marketed by the manufacturer or importer:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for a PMA, the manufacturer shall submit the appropriate reports required by the MDR Regulation within the time frames as identified in 21 CFR 803.10(c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health. The manufacturer is responsible for submitting a baseline report on FDA Form 3417 for a device when the device model is first reported under 21 CFR 803.50. This baseline report is to include the PMA reference number. Any written report and its envelope is to be specifically identified, e.g., "Manufacturer Report," "5-Day Report," "Baseline Report," etc.

Any written report is to be submitted to:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
PO Box 3002
Rockville, Maryland 20847-3002

Copies of the MDR Regulation (FOD # 336&1336) and FDA publications entitled "An Overview of the Medical Device Reporting Regulation" (FOD # 509) and "Medical Device Reporting for Manufacturers" (FOD #987) are available on the CDRH WWW Home Page. They are also available through CDRH's Fact-On-Demand (F-O-D) at 800-899-0381. Written requests for information can be made by sending a facsimile to CDRH's Division of Small Manufacturers International and Consumer Assistance (DSMICA) at 301-443-8818.

7

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Our Reference No. 96-1408

December 16, 1997

Ms. Joan F. Roelands
OMJ Pharmaceuticals, Inc.
Carr. #2, Km 45.6
Bo. Campo Alegre
Manati, Puerto Rico 00674

Dear Ms. Roelands:

Your biologics license application for Becaplermin is approved effective this date. OMJ Pharmaceuticals, Inc., Manati, Puerto Rico, is hereby authorized to manufacture and ship for sale, barter, or exchange in interstate and foreign commerce Becaplermin under Department of Health and Human Services Biologics License No. 1196.

Becaplermin is indicated for treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond, and have adequate blood supply.

Under this authorization, you are approved to manufacture Becaplermin utilizing Becaplermin Concentrate manufactured by Chiron Corporation (Biologics License No. 1106) under a shared manufacturing arrangement. Any addition or deletion of establishments involved in the shared manufacturing arrangement will require the submission of appropriate supporting data in order to ensure continued compliance with the approved standards for the manufacture of Becaplermin.

In accordance with approved labeling, your product will be distributed by McNeil Pharmaceutical under the tradename Regranex, and will be marketed as a gel formulation in 2, 7.5 and 15 gram fill sizes.

You are not currently required to submit samples of future lots of this product to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2. FDA will continue to monitor compliance with 21 CFR 610.1 requiring assay and release of only those lots that meet release specifications.

The dating period for this product shall be 9 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of formulation of the final gel product. Results of ongoing stability studies should be submitted throughout the dating period as they become available including the results of stability studies from the first three production lots.

We acknowledge your written commitments dated December 15, 1997 to:

1. Identify (in conjunction with RWJPRI) with due diligence the cause for the change in the stability profile observed with the finished drug product. After sufficient data are collected and analyzed, submit the conclusions of the investigation to the Agency.

2. Place [redacted] batches of Becaplermin on stability program at 5°C (2-8°C). Place at least one production batch per tube size on stability each month that particular tube size is manufactured from November, 1997 to September, 1998. If the 2, 7.5 and 15g tube sizes are all manufactured within the same month, then only the 2 and 15g tube sizes will be placed on stability to bracket the results.

(b)(4)

3. Continuously monitor the temperature of product shipments from OMJ Pharmaceuticals, Inc., [redacted] Puerto Rico, to the [redacted] Distribution Center, [redacted] [redacted] Real time, freeze/thaw, and accelerated temperature stability data will be collected from 3 lots of product to document the long term stability following temperature excursions. Until additional stability data are gathered, samples from any lot exposed to temperatures outside 2-8°C will not be commercially distributed without agency concurrence and if released, samples will be placed on a stability study.

(b)(4)

4. Validate shipping of stability samples sent to Chiron Corporation and to discard any samples exposed to temperatures outside of the specified range.

5. Manufacture a [redacted] lot of product for which the thawed drug substance was held for 18 days. This lot will be entered into the stability program.

(b)(4)

6. We also acknowledge additional information in your letter of December 15, 1997, addressing the agency's observations noted during the April 28 - May 7, 1997, preapproval inspection and your commitment to provide further information and data within the timelines specified.

7. In addition, we acknowledge your letter of December 11, 1997 in which you commit to submitting to CBER final reports of the clinical studies for Becaplermin in venous stasis and pressure ulcers.

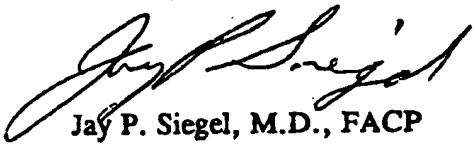
Any changes in the supplier of Becaplermin Concentrate, or in the manufacture, packaging or labeling of the product or in the manufacturing facilities will require the submission of information to your biologics license application for our review and written approval consistent with 21 CFR 601.12.

It is requested that adverse experience reports be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). All adverse experience

reports should be prominently identified according to 21 CFR 600.80 and be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

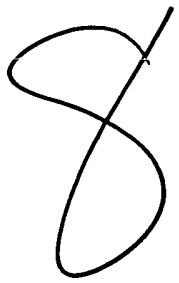
Please submit three copies of all final printed labeling at the time of use and include part II of the label transmittal form with completed implementation information. In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2567 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Staff, HFM-202, 1401 Rockville Pike, Rockville, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by an FDA Form 2567. All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other similar products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Sincerely yours,



Jay P. Siegel, M.D., FACP
Director
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

cc: Jacqueline Coelln/RWJPRI



REGRANEX® GEL 0.01%
(becaplermin)

DESCRIPTION
REGRANEX® Gel contains becaplermin, a recombinant human platelet-derived growth factor (rhPDGF-BB) for topical administration. Becaplermin is produced by recombinant DNA technology by insertion of the gene for the B chain of platelet-derived growth factor (PDGF) into the yeast, *Saccharomyces cerevisiae*. Becaplermin has a molecular weight of approximately 25 KD and is a homodimer composed of two identical polypeptide chains that are bound together by disulfide bonds. Becaplermin Concentrate is produced by Chiron Corp. and supplied to OMJ Pharmaceuticals under a shared manufacturing arrangement. REGRANEX Gel is a non-sterile, low bioburden, preserved, sodium carboxymethylcellulose-based (CMC) topical gel, containing the active ingredient becaplermin and the following inactive ingredients: sodium chloride, sodium acetate trihydrate, glacial acetic acid, water for injection, and methylparaben, propylparaben, and m-cresol as preservatives and L-lysine hydrochloride as a stabilizer. Each gram of REGRANEX Gel contains 100 µg of becaplermin.

CLINICAL PHARMACOLOGY
REGRANEX has biological activity similar to that of endogenous platelet-derived growth factor, which includes promoting the chemotactic recruitment and proliferation of cells involved in wound repair and enhancing the formation of granulation tissue.

Pharmacokinetics
Ten patients with Stage III or IV (as defined in the International Association of Enterostomal Therapy (IAET) guide to chronic wound staging, *J. Enterostomal Ther* 15:4, 1988 and *Decubitis* 2:24, 1989) lower extremity diabetic ulcers received topical applications of becaplermin gel 0.01% at a dose range of 0.32-2.95 µg/kg (7 µg/cm²) daily for 14 days. Six patients had non-quantifiable PDGF levels at baseline and throughout the study, two patients had PDGF levels at baseline which did not increase substantially, and two patients had PDGF levels that increased sporadically above their baseline values during the 14 day study period.

Systemic bioavailability of becaplermin was less than 3% in rats with full thickness wounds receiving single or multiple (5 days) topical applications of 127 µg/kg (20.1 µg/cm² of wound area) of becaplermin gel.

Clinical Studies
The effects of REGRANEX Gel on the incidence of and time to complete healing in lower extremity diabetic ulcers were assessed in four randomized controlled studies. Of 922 patients studied, 478 received either REGRANEX Gel 0.003% or 0.01%. All study participants had lower extremity diabetic neuropathic ulcers that extended into the subcutaneous tissue or beyond (Stages III and IV of the IAET guide to chronic wound staging). Ninety-three percent of the patients enrolled in these four trials had foot ulcers. The remaining 7% of the patients had ankle or leg ulcers. The diabetic ulcers were of at least 8 weeks duration and had an adequate blood supply (defined as T_cpO_2 > 30 mm Hg). In the four trials, ninety-five percent of the ulcers measured in area up to 10 cm², and the median ulcer size at baseline ranged from 1.4 cm² to 3.5 cm². All treatment groups received a program of good ulcer care consisting of initial complete sharp debridement, a non-weight-bearing regimen, systemic treatment for wound-related infection if present, moist saline dressings changed twice a day, and additional debridement as necessary. REGRANEX Gel 0.003% or 0.01% or placebo gel was applied once a day and covered with a saline moistened dressing. After approximately 12 hours, the gel was gently rinsed off and a saline moistened dressing was then applied for the remainder of the day. Patients were treated until complete healing, or for a period of up to 20 weeks. Patients were considered a treatment failure if their ulcer did not show an approximately 30% reduction in initial ulcer area after eight to ten weeks of REGRANEX Gel therapy.

The primary endpoint, incidence of complete ulcer closure within 20 weeks, for all treatment arms is shown in Figure 1. In each study, REGRANEX Gel in conjunction with good ulcer care was compared to placebo gel plus good ulcer care or good ulcer care alone.

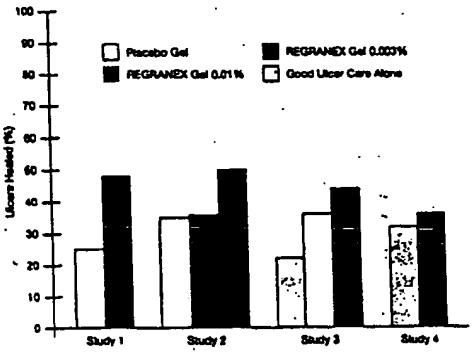
In Study 1, a multicenter, double-blind, placebo controlled trial of 118 patients, the incidence of complete ulcer closure for REGRANEX Gel 0.003% (n=61) was 48% versus 25% for placebo gel (n=57; p=0.02, logistic regression analysis).

In Study 2, a multicenter, double-blind, placebo controlled trial of 382 patients, the incidence of complete ulcer closure for REGRANEX Gel 0.01% (n=123), was 50% versus 36% for REGRANEX Gel 0.003% (n=132), and 35% for placebo gel (n=127). Only REGRANEX Gel 0.01% was significantly different from placebo gel (p=0.01, logistic regression analysis).

The primary goal of Study 3, a multicenter controlled trial of 172 patients, was to assess the safety of vehicle gel (placebo; n=70) compared to good ulcer care alone (n=68). The study included a small (n=34) REGRANEX Gel 0.01% arm. Incidences of complete ulcer closure were 44% for REGRANEX Gel, 36% for placebo gel and 22% for good ulcer care alone.

In Study 4, a multicenter, evaluator-blind, controlled trial of 250 patients, the incidences of complete ulcer closure in the REGRANEX Gel 0.01% arm (n=128) (36%) and good ulcer care alone (n=122) (32%) were not statistically different.

Figure 1: Incidence of Complete Healing



In general, where REGRANEX Gel was associated with higher incidences of complete ulcer closure, differences in the incidence first became apparent after approximately 10 weeks and increased with continued treatment (Table 1).

Table 1: Life Table Estimates of the Incidence (%) of Complete Healing Over Time for Study 2

	REGRANEX Gel 0.01% (%)	Placebo Gel (%)
Week 2	1	0
Week 4	8	2
Week 6	9	6
Week 8	16	14
Week 10	23	18
Week 12	34	25
Week 14	37	28
Week 16	43	33
Week 18	46	34
Week 20	50	37

In a 3-month follow-up period where no standardized regimen of preventative care was utilized, the incidence of ulcer recurrence was approximately 30% in all treatment groups, demonstrating that the durability of ulcer closure was comparable in all treatment groups.

The efficacy of REGRANEX Gel for the treatment of non-diabetic ulcers is under evaluation.

INDICATIONS AND USAGE
REGRANEX Gel is indicated for the treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. When used as an adjunct to, and not a substitute for, good ulcer care practices including initial sharp debridement, pressure relief and infection control, REGRANEX Gel increases the incidence of complete healing of diabetic ulcers.

The efficacy of REGRANEX Gel for the treatment of diabetic neuropathic ulcers that do not extend through the dermis into subcutaneous tissue (Stage I or II, IAET staging classification) or ischemic diabetic ulcers has not been evaluated.

CONTRAINDICATIONS
REGRANEX Gel is contraindicated in patients with:
- known hypersensitivity to any component of this product (e.g., parabens);
- known neoplasm(s) at the site(s) of application.

635-10-240-1

REGRANEX® GEL 0.01%
(becaplermin)

102401

WARNINGS
REGRANEX (becaplermin) Gel is a non-sterile, low bioburden preserved product. Therefore, it should not be used in wounds that close by primary intention.

PRECAUTIONS
For external use only.

If application site reactions occur, the possibility of sensitization or irritation caused by parabens or m-cresol should be considered.

The effects of becaplermin on exposed joints, tendons, ligaments, and bone have not been established in humans. In pre-clinical studies, rats injected at the metatarsals with 3 or 10 µg/site (approximately 60 or 200 µg/kg) of becaplermin every other day for 13 days displayed histological changes indicative of accelerated bone remodeling consisting of periosteal hyperplasia and subperiosteal bone resorption and exostosis. The soft tissue adjacent to the injection site had fibroplasia with accompanying mononuclear cell infiltration reflective of the ability of PDGF to stimulate connective tissue growth.

Information for Patients
Patients should be advised that:
- hands should be washed thoroughly before applying REGRANEX Gel;
- the tip of the tube should not come into contact with the ulcer or any other surface; the tube should be recapped tightly after each use;
- a cotton swab, tongue depressor, or other application aid should be used to apply REGRANEX Gel;
- REGRANEX Gel should only be applied once a day in a carefully measured quantity (see Dosage and Administration section). The measured quantity of gel should be spread evenly over the ulcerated area to yield a thin continuous layer of approximately ¼ of an inch thickness. The measured length of the gel to be squeezed from the tube should be adjusted according to the size of the ulcer. The amount of REGRANEX Gel to be applied daily should be recalculated at weekly or biweekly intervals by the physician or wound care giver;

Step-by-step instructions for application of REGRANEX Gel are as follows:
  - Squeeze the calculated length of gel on to a clean, firm, non-absorbable surface, e.g., wax paper.
  - With a clean cotton swab, tongue depressor, or similar application aid, spread the measured REGRANEX Gel over the ulcer surface to obtain an even layer.
  - Cover with a saline moistened gauze dressing.
- after approximately 12 hours, the ulcer should be gently rinsed with saline or water to remove residual gel and covered with a saline-moistened gauze dressing (without REGRANEX Gel);
- It is important to use REGRANEX Gel together with a good ulcer care program, including a strict non-weight-bearing program;
- excess application of REGRANEX Gel has not been shown to be beneficial;
- REGRANEX Gel should be stored in the refrigerator. Do not freeze REGRANEX Gel;
- REGRANEX Gel should not be used after the expiration date on the bottom, crimped end of the tube.

Drug Interactions
It is not known if REGRANEX Gel interacts with other topical medications applied to the ulcer site. The use of REGRANEX Gel with other topical drugs has not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Becaplermin was not genotoxic in a battery of *in vitro* assays, (including those for bacterial and mammalian cell point mutation, chromosomal aberration, and DNA damage/repair). Becaplermin was also not mutagenic in an *in vivo* assay for the induction of micronuclei in mouse bone marrow cells.

Carcinogenesis and reproductive toxicity studies have not been conducted with REGRANEX Gel.

Pregnancy: Category C
Animal reproduction studies have not been conducted with REGRANEX Gel. It is also not known whether REGRANEX Gel can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. REGRANEX Gel should be given to pregnant women only if clearly needed.

Nursing Mothers
It is not known whether becaplermin is excreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when REGRANEX Gel is administered to nursing women.

Pediatric Use
Safety and effectiveness of REGRANEX Gel in pediatric patients below the age of 16 years have not been established.

ADVERSE REACTIONS
Patients receiving REGRANEX Gel, placebo gel, and good ulcer care alone had a similar incidence of ulcer-related adverse events such as infection, cellulitis, or osteomyelitis. However, erythematous rashes occurred in 2% of patients treated with REGRANEX Gel and placebo, and none in patients receiving good ulcer care alone. The incidence of cardiovascular, respiratory, musculoskeletal and central and peripheral nervous system disorders was not different across all treatment groups. Mortality rates were also similar across all treatment groups. Patients treated with REGRANEX Gel did not develop neutralizing antibodies against becaplermin.

DOSAGE AND ADMINISTRATION
The amount of REGRANEX Gel to be applied will vary depending upon the size of the ulcer area. To calculate the length of gel to apply to the ulcer, measure the greatest length of the ulcer by the greatest width of the ulcer in either inches or centimeters. To calculate the length of gel in inches, use the formula shown below in Table 2, and to calculate the length of gel in centimeters, use the formula shown below in Table 3.

Table 2: Formula to Calculate Length of Gel in Inches to be Applied Daily

INCHES

Tube Size	Formula
15 or 7.5g tube	length X width X 0.6
2g tube	length X width X 1.3

Using the calculation, each square inch of ulcer surface will require approximately ⅝ inch length of gel squeezed from a 15g or 7.5g tube, or approximately 1⅓ inch length of the gel from a 2g tube. For example, if the ulcer measures 1 inch by 2 inches, then a 1¼ inch length of gel should be used for 15g or 7.5g tubes (1 X 2 X 0.6 = 1¼) and 2⅝ inch gel length should be used for 2g tube (1 X 2 X 1.3 = 2⅝).

Table 3: Formula to Calculate Length of Gel in Centimeters to be Applied Daily

CENTIMETERS

Tube Size	Formula
15 or 7.5g tube	length X width ÷ 4
2g tube	length X width ÷ 2

Using the calculations for ulcer size in centimeters, each square centimeter of ulcer surface will require approximately a 0.25 centimeter length of gel squeezed from a 15g or 7.5g tube, or approximately a 0.5 centimeter length of gel from a 2g tube. For example, if the ulcer measures 4 cm by 2 cm, then a 2 centimeter length of gel should be used for 15g or 7.5g tube [(4 X 2) ÷ 4 = 2] and a 4 centimeter length of gel should be used for 2g tube [(4 X 2) ÷ 2 = 4].

The amount of REGRANEX Gel to be applied should be recalculated by the physician or wound care giver at weekly or biweekly intervals depending on the rate of change in ulcer area. The weight of REGRANEX Gel from 7.5g and 15g tubes is 0.85g per inch length and 0.25g per centimeter length.

To apply REGRANEX Gel, the calculated length of gel should be squeezed on to a clean measuring surface, e.g., wax paper. The measured REGRANEX Gel is transferred from the clean measuring surface using an application aid and then spread over the entire ulcer area to yield a thin continuous layer of approximately ¼ of an inch thickness. The site(s) of application should then be covered by a saline moistened dressing and left in place for approximately 12 hours. The dressing should then be removed and the ulcer rinsed with saline or water to remove residual gel and covered again with a second moist dressing (without REGRANEX Gel) for the remainder of the day. REGRANEX Gel should be applied once daily to the ulcer until complete healing has occurred. If the ulcer does not decrease in size by approximately 30% after 10 weeks of treatment or complete healing has not occurred in 20 weeks, continued treatment with REGRANEX Gel should be reassessed. The step-by-step instructions for applying REGRANEX Gel for home administration are described under "Information for Patients".

HOW SUPPLIED
REGRANEX (becaplermin) Gel, supplied as a clear, colorless to straw-colored preserved gel containing 100µg of becaplermin per gram of gel, is available in multi-use tubes in the following sizes:

2g tubes	NDC 0045-0810-02
7.5g tubes	NDC 0045-0810-07
15g tubes	NDC 0045-0810-15

REGRANEX Gel is for external use only.

Storage
Store refrigerated; 2-8°C (36-46°F). DO NOT FREEZE. DO NOT USE THE GEL AFTER THE EXPIRATION DATE AT THE BOTTOM OF THE TUBE.

Caution: Federal (USA) law prohibits dispensing without prescription.

U.S. Patent #5,457,093

McNEIL PHARMACEUTICAL

Distributed by:
McNEIL PHARMACEUTICAL
Raritan, New Jersey 08869

Manufactured by:
OMJ Pharmaceuticals, Inc.
U.S. License No. 1196
San German, Puerto Rico 00683

Becaplermin Concentrate provided by: Chiron Corp.,
U.S. License No. 1106, Emeryville, CA 94608

Issued January 1998

835-10-240-1

9

PATENT
Atty Ref. No. 273802801100

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

I hereby certify that this paper or fee is being deposited on February 13, 1998 with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. § 1.10 as Express Mail Label No. EM056839453US and is addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

2/13/98
Date

Robyn Leiner
Robyn Leiner

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Murray et al.

Patent No.: 4,845,075

Issued: July 4, 1989

For: BIOLOGICALLY ACTIVE B-CHAIN HOMODIMERS

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. SECTION 156

Commissioner for Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

Dear Sir:

In accordance with 35 U.S.C. Section 156, Applicant, ZymoGenetics, Inc., a corporation of the State of Washington, having a place of business at 1201 Eastlake Avenue East, Seattle, Washington, 98102, (hereinafter "Applicant") represents that it is the assignee of the entire interest in and to Letters Patent of the United States No. 4,845,075, granted to Mark Murray and James Kelly for BIOLOGICALLY ACTIVE B-CHAIN HOMODIMERS by virtue of an assignment in favor of ZymoGenetics, recorded on February 26, 1987, on Reel 4694, Frame 0991, and by virtue of an assignment for U.S. Patent Application No. 06/705,175, filed February 25, 1985, directed to

EXPRESSION OF BIOLOGICALLY ACTIVE PDGF ANALOGS IN EUCARYOTIC CELLS, recorded on October 21, 1985, on Reel 4469, Frame 0438.

Applicant, through undersigned counsel, hereby applies for a 4.36 year (1593 day) extension of the term of United States Patent No. 4,845,075 under 35 U.S.C. § 156 on the basis of the following information submitted in accordance with the provisions of Title 37 C.F.R. § 1.740(a) (1)-(17), set forth in the sequence of those subparagraphs. Filed herewith is a Certificate under 37 C.F.R. § 3.73(b) and a Power of Attorney authorizing the undersigned to file and prosecute this Application for Extension of Patent Term, and to transact all business in relations thereto (EXHIBIT 1).

(1) This application for extension is based upon the regulatory review period before the FDA for the approved products, "Becaplermin Concentrate" and "REGRANEX® Gel" (hereinafter "REGRANEX®"). REGRANEX® contains becaplermin, a recombinant human platelet-derived growth factor composed of two disulfide-linked B-chain polypeptides (rhPDGF-BB) for topical administration. Becaplermin Concentrate is produced by Chiron Corporation and supplied to OMJ Pharmaceuticals, Inc., an affiliate of Ortho-McNeil Pharmaceutical Corporation, a wholly owned subsidiary of Johnson & Johnson under a shared manufacturing agreement. Letters of authorization executed by the marketing applicants to the patent assignee are attached as EXHIBIT 2. REGRANEX®, is a non-sterile, low bioburden, preserved, sodium carboxymethylcellulose based (CMC) topical gel, containing the active ingredient becaplermin and the following inactive ingredients: sodium chloride, sodium acetate trihydrate, glacial acetic acid, water for injection, and methylparaben, propylparaben, and m-cresol as preservatives and l-lysine hydrochloride as a stabilizer. Each gram of REGRANEX® contains 100µg of becaplermin and is indicated for use in the treatment of diabetic ulcers as further described in attached EXHIBIT 3 (which is the package insert for this product).

(2) The approved products were subject to regulatory review under Public Health Service Act, Section 351 (42 U.S.C. § 262).

(3) The approved products, "Becaplermin Concentrate" (Biologics License No. 1106) and "REGRANEX®" (Biologics License No. 1196) received permission for commercial marketing or use after a regulatory review period under Public Health Service Act, Section 351 (42 U.S.C. § 262) on December 16, 1997.

(4) The active ingredient in "Becaplermin Concentrate" and "REGRANEX®" is a recombinant form of human platelet-derived growth factor composed of two disulfide-linked B chain polypeptides (rhPDGF-BB). To the best of Applicant's knowledge, the permission for the commercial marketing or use of this product after such regulatory review period is the first permitted commercial marketing or use of such product under the Public Health Service Act.

(5) This Application for extension of patent term under 35 U.S.C. Section 156, is being submitted within the permitted 60 day period, which period will expire on February 13, 1998.

(6) The complete identification of the patent for which extension is being sought is as follows:

U.S. Patent No.:	4,845,075
Issue Date:	July 4, 1989
Expires:	July 4, 2006
Inventors:	Mark MURRAY and James KELLY

(7) A copy of the patent for which an extension is being sought, including the entire specification and claims, is attached as EXHIBIT 4.

(8) A receipt of maintenance fee payment has been issued with regard to U.S. Patent No. 4,845,075. A copy of the maintenance fee receipt is attached as EXHIBIT 5. No disclaimer, certificate of correction or reexamination certificate has been issued in connection with U.S. Patent No. 4,845,075.

(9) U.S. Patent No. 4,845,075, for which this extension is sought, generally claims proteins having two polypeptide chains, each of the chains comprising the amino acid sequence of the B-chain of PDGF and segments thereof, compositions comprising effective amounts of proteins derived from rhPDGF-BB, and methods for enhancing the wound healing process comprising administering such compositions. The active ingredient in the approved products, "Becaplermin Concentrate" and "REGRANEX®", is a recombinant form of human platelet-derived growth factor composed of two disulfide-linked B chain polypeptides (rhPDGF-BB). The approved product is indicated for the treatment of diabetic ulcers.

Claims 1-6:

1. An isolated protein having two polypeptide chains, each of said chains comprising the amino acid sequence of the B-chain of PDGF from amino acid 15 to amino acid 109.

2. An isolated protein having two polypeptide chains, each of said chains comprising the amino acid sequence of the B-chain of PDGF from amino acid 29 to amino acid 109.

3. An isolated protein having two polypeptide chains, each of said chains comprising the amino acid sequence of the B-chain of PDGF from amino acid 15 to amino acid 101.

4. An isolated protein having two polypeptide chains, each of said chains comprising the amino acid sequence of the B-chain of PDGF from amino acid 29 to amino acid 101.

5. An isolated protein having two polypeptide chains, each of said chains comprising the amino acid sequence of the B-chain of PDGF from amino acid 1 to amino acid 101.

6. An isolated protein having two polypeptide chains, each of said chains comprising the amino acid sequence of the B-chain of PDGF from amino acid 1 to amino acid 109.

* * * * *

The approved products are "Becaplermin Concentrate" and "REGRANEX®". The active ingredient in the approved products is a homodimer composed of two disulfide-linked B-chain polypeptides of PDGF. Claims 1-6 claim an isolated protein having two polypeptide chains, each of the chains comprising the amino acid sequence of the B-chain of PDGF and segments thereof. Thus, claims 1-6 read on the approved products, "Becaplermin Concentrate" and "REGRANEX®".

Claims 7-12:

7. An isolated protein having two polypeptide chains, each of said chains comprising the amino acid sequence of p28-sis corresponding to the B-chain of PDGF from amino acid 15 to amino acid 109.

8. An isolated protein having two polypeptide chains, each of said chains comprising the amino acid sequence of p28-sis corresponding to the B-chain of PDGF from amino acid 29 to amino acid 109.

9. An isolated protein having two polypeptide chains, each of said chains comprising the amino acid sequence of p28-sis corresponding to the B-chain of PDGF from amino acid 15 to amino acid 101.

10. An isolated protein having two polypeptide chains, each of said chains comprising the amino acid sequence of p28-sis corresponding to the B-chain of PDGF from amino acid 29 to amino acid 101.

11. An isolated protein having two polypeptide chains, each of said chains comprising the amino acid sequence of p28-sis corresponding to the B-chain of PDGF from amino acid 1 to amino acid 101.

12. An isolated protein having two polypeptide chains, each of said chains comprising the amino acid sequence of p28-sis corresponding to the B-chain of PDGF from amino acid 1 to amino acid 109.

* * * * *

The approved products are "Becaplermin Concentrate" and "REGRANEX®". The active ingredient in the approved products is a homodimer composed of two disulfide-linked B-chain polypeptides. Claims 7-12 claim an isolated protein having two polypeptide chains, each of the chains comprising the amino acid sequence of p28-sis corresponding to the B-chain of PDGF and segments thereof. p28-sis, derived from the v-sis gene, has a high degree of homology with the B-chain of PDGF differing at only four positions: 6, 7, 101 and 107. These amino acid differences are largely conservative and do not effect the biological activity of the B-chain. Thus, claims 7-12 read on the approved products.

Claim 13:

13. A wound-healing composition comprising a therapeutically effective amount of an isolated protein according to any one of claims 1-12, and a physiologically acceptable carrier or diluent.

* * * * *

The approved product "REGRANEX®" is a wound-healing composition. It contains a therapeutically effective amount of an isolated protein having two polypeptide chains, each of the chains comprising the amino acid sequence of the B-chain of PDGF and segments thereof. It is administered in an acceptable carrier or diluent as described in the insert (EXHIBIT 3). Thus, claim 13 reads on the approved product.

Claim 15:

15. The wound-healing composition of claim 13 including an adjuvant.

* * * * *

The approved product "REGRANEX®" includes an adjuvant, including for example, L-lysine which is a stabilizing substance. Thus, claim 13 reads on the approved product.

Claim 17:

17. A method for enhancing the wound healing process in a warm-blooded animal, comprising administering to the animal a composition according to any one of the claims 13-16.

* * * * *

The approved product "REGRANEX®" is a composition according to claim 13 and 15 to be administered to humans to promote the chemotactic recruitment and proliferation of cells involved in wound repair, specifically to increase the incidence of complete healing of diabetic ulcers, in accordance with the approved package insert (EXHIBIT 3). Thus, claim 17 reads on the approved product.

(10) The relevant dates and information pursuant to 35 U.S.C. § 156 (g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(a) Issue date of patent: July 4, 1989

(b) Effective Date of BB IND No. 3486 application: March 30, 1990

Date BB IND No. 3486 submitted: March 30, 1990

Date BB IND No. 3486 received by the FDA: March 30, 1990

(c) Date BLA No. 96-1408 (REGRANEX) submitted: Dec. 16, 1996

Date BLA No. 96-1422 (Becaplermin Concentrate) submitted: Dec. 16, 1996

Date BLA No. 96-1408 (REGRANEX) received: Dec. 16, 1996

Date BLA No. 96-1422 (Becaplermin Concentrate) received: Dec. 16, 1996

(d) Date BLA No. 96-1408 (REGRANEX) approved: Dec. 16, 1997

Date BLA No. 96-1422 (Becaplermin Concentrate) approved: Dec. 16, 1997

(11) A brief description of the significant activities undertaken by the marketing applicants, OMJ Pharmaceuticals, Inc., an affiliate of Ortho-McNeil Pharmaceutical Corporation, a wholly owned subsidiary of Johnson & Johnson, and Chiron Corporation, on behalf of the Applicant during the applicable regulatory review period with respect to the approved product, and the significant dates applicable to such activities, are set out in EXHIBIT 6.

(12) Applicant is of the opinion that U.S. Patent No. 4,845,075, is eligible for extension under 35 U.S.C. § 156 because it satisfies all the requirements for such an extension in as much as:

(i) the term of such patent has not expired before submission of this application (35 U.S.C. § 156(a)(1));

(ii) the term of such patent has never been extended (35 U.S.C. § 156(a)(2));

(iii) the application for extension is submitted by the owner of record, through undersigned counsel, in accordance with the requirements of 35 U.S.C. § 156(d);

(iv) the approved products, "Becaplermin Concentrate" and "REGRANEX®" have been subject to a regulatory review period before its commercial marketing or use (35 U.S.C. § 156(a)(4));

(v) the permission for the commercial marketing or use of the products, "Becaplermin Concentrate" and "REGRANEX®", after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of the Public Health Service Act under which such regulatory period occurred (35 U.S.C. § 156 (a)(5)(a)); and

(vi) no other patent has been extended for the same regulatory review period for the approved product (35 U.S.C. § 156(c)(4)).

Applicant requests an extension of the patent term of U.S. Patent No. 4,845,075 by 4.36 years (1593 days) from the original expiration date of July 4, 2006 to November 14, 2010. This period of extension is calculated according to the following subsections of 37 C.F.R. § 1.775:

(a) The original expiration date of the Patent is 17 years from the date of issue, that is July 4, 2006.

(c) The length of the regulatory review period was 2819 days, calculated as follows:

(1) The number of days from the effective date of original IND (BB) No. 3486 for the approved products, "REGRANEX®" and "Becaplermin Concentrate" to the receipt by the FDA of BLA No. 96-1408

(REGRANEX) and BLA No. 96-1422 (Becaplermin Concentrate), i.e., from March 30, 1990 to December 16, 1996 is 2453 days.

(2) The number of days between initial submission of the BLA No. 96-1408 (REGRANEX) and BLA No. 96-1422 (Becaplermin Concentrate) to the approval of the BLA's, that is from December 16, 1996 to December 16, 1997, is 366 days.

(d) The term of the patent as extended from a human drug product is to November 14, 2010, that is an extension of 1593 days, calculated by subtracting 1226 days from the 2819 days of the total regulatory review period from subparagraph (c):

(1) From the number of days of the regulatory review period calculated under subparagraph (c), the following are subtracted:

i) no part of the regulatory period was before the date on which the patent issued;

(ii) the number of days in the regulatory period as set forth in §1.775(c)(1) and §1.775(c)(1)(2) during which the marketing applicants on behalf of the Applicant, did not act with due diligence, which is zero (0) days; and

(iii) One-half the number of days remaining in the period as set forth in §1.775(c)(1) after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii), which is 1226 days (§ 1.775(c)(1) 2453 days ÷ 2 = 1226 days).

(2) Adding 1593 days to the original expiration date of July 4, 2006, comes to November 14, 2010.

(3) Adding 14 year to the date of approval of the BLA's comes to December 16, 2011.

(4) The earlier of the dates calculated under the subparagraphs (d)(2) and (3) above is November 14, 2010.

(5)(i) The original patent was issued after September 24, 1984. Adding 5 years to the original expiration date of the patent comes to July 4, 2011. The earlier of the dates calculated under the subparagraphs (d)(4) and (d)(5(i)) above is November 14, 2010.

(6) The original patent was not issued before September 24, 1984, so this paragraph is not applicable.

(13) Applicant, through its undersigned counsel, acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determinations to be made relative to the application for extension, in accordance with 37 C.F.R. § 1.765.

(14) A check in the amount of $1120, payable to the Commissioner of Patents and Trademarks is attached to cover the fee prescribed by 37 C.F.R. 1.20(j)(1) for receiving and acting upon this application for extension. If any additional fees are due, authorization is given to charge our deposit account number 03-1952.

(15) Please direct all inquiries and correspondence relating to this application for patent term extension to:

Gladys H. Monroy

Morrison & Foerster
755 Page Mill Road
Palo Alto, CA 94304
Phone: (650) 813-5711
Fax: (650) 494-0792

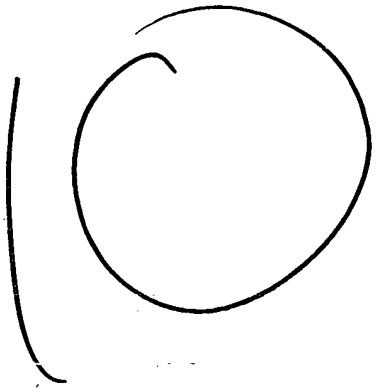
(16) Submitted herewith is a certification that these application papers are being submitted in duplicate (EXHIBIT 7).

(17) Additionally submitted herewith is a Declaration of Gladys H. Monroy as patent counsel for Applicant pursuant to 37 CFR § 1.740 (b)(1) as authorized by the Power of Attorney executed by Applicant submitted herewith as EXHIBIT 8.

Respectfully submitted,

By: Gladys H. Monroy
Gladys H. Monroy
Registration No. 32,430

Morrison & Foerster
755 Page Mill Road
Palo Alto, CA 94304-1018
Direct: (650) 813-5711
Fax: (650) 494-0792



FDA U.S. Food and Drug Administration — Department of Health and Human Services

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

Note: this medical device has supplements. The device description may have changed. Be sure to look at the supplements to get an up-to-date view of this device.

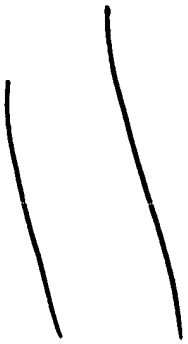
Premarket Approval (PMA) Database

Trade Name	PERI-OSS
Classification Name	Bone Grafting Material, For Dental Bone Repair
Generic Name	Calcium Phosphate-Ceramic
Regulation Number	872.3930
Applicant	CURASAN AG
PMA Number	P800035
Date Received	06/12/1980
Decision Date	03/24/1981
Product Code	LPK
Notice Date	04/13/1981
Advisory Committee	Dental
Expedited Review Granted?	No

Supplements:

S001 S002 S003 S004 S005 S007 S008 S010 S011

Database Updated 11/07/2005



DEC 14 2000

K994337

510(k) Summary
Vitoss™ Scaffold Synthetic Cancellous Bone Void Filler

Submitted by	Address	Telephone	Contact Person
Orthovita, Inc.	45 Great Valley Parkway Malvern, PA 19355	(610) 640-1775	Angie Ide Director, Regulatory Affairs

	Subject Device	Predicate Device
Trade Name	*Vitoss*™ Scaffold Synthetic Cancellous Bone Void Filler	Pro Osteon 500$_R$ Resorbable Bone Void Filler
Common Name	Bone Void Filler	Bone Void Filler
Classification Name	Filler, Calcium Sulfate Preformed Pellets	Filler, Calcium Sulfate Preformed Pellets

Device Description:

Vitoss Scaffold is a porous calcium phosphate resorbable bone void filler for the repair of bony defects. It is an osteoconductive porous implant with a trabecular structure that resembles the multidirectional interconnected porosity of human cancellous bone. Pore diameters in the scaffold range from 1 μm to 1000 μm (1 mm). The implant is provided sterile in block and morsel forms.

Vitoss Scaffold guides the three-dimensional regeneration of bone in the defect site into which it is implanted. When *Vitoss* Scaffold is placed in direct contact with viable host bone, new bone grows in apposition to the calcium phosphate surfaces of the implant. As the implant resorbs, bone and other connective tissues grow into the space previously occupied by the scaffold. Results from animal studies demonstrate that eighty percent of *Vitoss* Scaffold is resorbed within twelve weeks.

Intended Use:

Vitoss Scaffold Synthetic Cancellous Bone Void Filler is intended only for use as a bone void filler for voids or gaps that are not intrinsic to the stability of the bony structure. *Vitoss* Scaffold is indicated for use in the treatment of surgically created osseous defects or osseous defects created from traumatic injury to the bone. *Vitoss* Scaffold should not be used to treat large defects that in the surgeon's opinion would fail to heal spontaneously.

Vitoss Scaffold is intended to be gently packed into bony voids or gaps of the skeletal system (i.e., the extremities, spine and pelvis). Following placement in the bony void

or gap, the calcium phosphate scaffold resorbs and is replaced with bone during the healing process.

Comparison to Predicate:

COMPARISON TO PREDICATE		
	Vitoss Scaffold	Pro Osteon 500R
Intended Use	Synthetic Bone Void Filler	Synthetic Bone Void Filler
Target Population	Individuals with bony defects resulting from surgery or trauma	Individuals with bony defects resulting from surgery or trauma
Anatomical Locations	Bony voids or gaps of the skeletal system, i.e., the extremities, spine and pelvis	Bony voids or gaps of the skeletal system, i.e., the extremities, spine and pelvis
Labeling	Labeling contains same intended use, contraindications, warnings, precautions, and adverse events as predicate	Labeling contains same intended use, contraindications, warnings, precautions, and adverse events as *Vitoss*
Materials		
Chemical Composition	Calcium salt	Calcium salts
Mineral Phase(s)	β-Tricalcium Phosphate $Ca_3(PO_4)_2$	Hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ Calcium Carbonate $CaCO_3$
Design		
Physical Structure	Trabecular structure similar to cancellous bone	Trabecular structure similar to cancellous bone
Porosity	Approximately 90%	Approximately 55%
Pore Size (range)	1-1000μm	280-779μm
Performance		
Osteoconductivity	Osteoconductive	Osteoconductive
Resorption	Demonstrated as 76% resorbed at six weeks and 86% resorbed at twelve weeks	Reported as 20% resorbed at six weeks and 45% resorbed at twelve weeks
Bone Remodeling (Recorded as ratio of bone in implant to adjacent bone)	Demonstrated as 0.6 at six weeks and 1.2 at twelve weeks	Demonstrated as 0.4 at six weeks and 0.5 at twelve weeks
Mechanical Strength	Does not impart mechanical strength to surgical site	Does not impart mechanical strength to surgical site
Sterility	Sterilized by gamma radiation, single use only	Sterilized by gamma radiation, single use only
Biocompatibility	Established	Established
Dosage Form(s)	Morsels (1-4 mm sizes) and blocks (9x23mm cylinder)	Morsels (1-4 mm sizes)

Non-clinical Performance Data:

Pre-clinical animal data demonstrate that *Vitoss* Scaffold supports bone growth into a metaphyseal defect. These data show that *Vitoss* Scaffold resorbs at an early time period, accompanied by early bone ingrowth and bone remodeling. These results, in conjunction with biocompatibility data, demonstrate that *Vitoss* Scaffold Bone Void Filler is as safe and as effective as the predicate device, Pro Osteon 500R.

Clinical Performance Data:

Calcium-based ceramic materials, including tricalcium phosphate, have been used in clinical practice for more than 25 years with no remarkable safety issues. Early successful results were achieved in dentistry and oral reconstructive surgery. Subsequently, successful results have been demonstrated in the treatment of many orthopedic problems, including filling defects secondary to trauma, benign tumors and cysts, and the filling of metaphyseal defects of long bones.

In terms of safety, calcium-based bone void fillers have the advantage of avoiding the potential morbidity associated with the harvesting of bone autografts and the potential for disease transmission by allografts. To date there have been no reports in the literature of adverse reactions to calcium-based ceramic materials. A review of FDA's Manufacturer and User Facility Device Experience Database (MAUDE), conducted on 12/13/1999, showed no records of adverse device experience with Pro Osteon 500R, the device to which *Vitoss* Scaffold claims substantial equivalence. Only two records were found reported for all devices with the product code MQV. These two records were for Wright Medical's product, Osteoset, the device to which Pro Osteon 500R was determined to be substantially equivalent. This confirms the continued safe use of the bone void fillers currently in commercial distribution.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

DEC 14 2000

Ms. Angie Ide
Director, Regulatory Affairs
Orthovita Company
45 Great Valley Parkway
Malvern, Pennsylvania 19355

Re: K994337
Trade Name: Vitoss™ Scaffold Synthetic Cancellous Bone Void Filler
Regulatory Class: Unclassified
Product Code: MQV
Dated: October 26, 2000
Received: October 27, 2000

Dear Ms. Ide:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4659. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address "http://www.fda.gov/cdrh/dsma/dsmamain.html."

Sincerely yours,

for Mark N. Melkerson

Celia M. Witten, M.D., Ph.D.
Director
Division of General, Restorative, and
Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

INDICATIONS FOR USE STATEMENT

510(k) Number: K994337

Device Name: *Vitoss™ Scaffold* Synthetic Cancellous Bone Void Filler

Indications For Use:

Vitoss Scaffold Synthetic Cancellous Bone Void Filler is intended only for use as a bone void filler for voids or gaps that are not intrinsic to the stability of the bony structure. *Vitoss* Scaffold is indicated for use in the treatment of surgically created osseous defects or osseous defects created from traumatic injury to the bone. *Vitoss* Scaffold should not be used to treat large defects that in the surgeon's opinion would fail to heal spontaneously.

Vitoss Scaffold is intended to be gently packed into bony voids or gaps of the skeletal system (i.e., the extremities, spine and pelvis). Following placement in the bony void or gap, the calcium phosphate scaffold resorbs and is replaced with bone during the healing process.

PLEASE DO NOT WRITE BELOW THIS LINE
CONTINUE ON ANOTHER PAGE IF NEEDED

Concurrence of CDRH, Office of Device Evaluation (ODE)

(Division Sign-Off)
Division of General Restorative Devices
510(k) Number K994337

Prescription Use _____ OR **Over-The-Counter Use** _____
(Per 21 CFR 801.109)

510(k) Premarket Notification Database

Device Classification Name	Filler, Bone Void, Calcium Compound
510(K) Number	K032409
Regulation Number	888.3045
Device Name	VITOSS SCAFFOLD SYNTHETIC CANCELLOUS BONE VOID FI
Applicant	ORTHOVITA, INC. 45 Great Valley Pkwy. Malvern, PA 19355
Contact	Andreina Ide
Classification Product Code	MQV
Date Received	08/04/2003
Decision Date	08/29/2003
Decision	Substantially Equivalent (SE)
Classification Advisory Committee	Orthopedic
Review Advisory Committee	Physical Medicine
Statement/Summary/Purged Status	Summary Only
Summary	Summary
Type	Traditional
Reviewed By Third Party	No
Expedited Review	No

Database Updated 11/07/2005

AUG 2 9 2003

K032409

510(k) Summary
Vitoss® *Scaffold* Synthetic Cancellous Bone Void Filler

Submitted by	Address	Telephone	Contact Person
Orthovita, Inc.	45 Great Valley Parkway Malvern, PA 19355	(610) 640-1775	Andreina Ide, Sr. Director, Regulatory Affairs

	Subject Device	Predicate Devices
Trade Name →	*Vitoss*® Scaffold Synthetic Cancellous Bone Void Filler	▪ WMT-TCP K022629 ▪ chronOS K013072
Common Name	Resorbable Synthetic Bone Void Filler/Bone Graft Substitute	
Classification Name	Resorbable Calcium Salt Bone Void Filler Device	

Device Description:

Vitoss Scaffold is a porous calcium phosphate resorbable bone void filler for the repair of bony defects. It is an osteoconductive porous implant with a trabecular structure that resembles the multidirectional interconnected porosity of human cancellous bone. Pore diameters in the scaffold range from 1 µm to 1000 µm (1 mm). The implant is provided sterile in block and morsel forms.

Vitoss Scaffold guides the three-dimensional regeneration of bone in the defect site into which it is implanted. When *Vitoss* Scaffold is placed in direct contact with viable host bone, new bone grows in apposition to the calcium phosphate surfaces of the implant. As the implant resorbs, bone and other connective tissues grow into the space previously occupied by the scaffold. Results from animal studies demonstrate that eighty percent of *Vitoss* Scaffold is resorbed within twelve weeks.

Intended Use:

Vitoss Scaffold Synthetic Cancellous Bone Void Filler is intended for use as a bone void filler for voids or gaps that are not intrinsic to the stability of the bony structure. *Vitoss* Scaffold is indicated for use in the treatment of surgically created osseous defects or osseous defects created from traumatic injury to the bone. *Vitoss* Scaffold should not be used to treat large defects that in the surgeon's opinion would fail to heal spontaneously.

Vitoss Scaffold is intended to be packed into bony voids or gaps of the skeletal system (i.e., the extremities, spine and pelvis) and may be combined with autogenous blood

and/or bone marrow. Following placement in the bony void or gap, the calcium phosphate scaffold resorbs and is replaced with bone during the healing process.

Comparison to Predicate:

	Vitoss Scaffold	MIIG-II-CP	ChronOS
Intended Use	Resorbable Synthetic Bone Void Filler	Resorbable Synthetic Bone Void Filler	Resorbable Synthetic Bone Void Filler
Target Population	Individuals with bony defects resulting from surgery or trauma	Individuals with bony defects resulting from surgery or trauma	Individuals with bony defects resulting from surgery or trauma
Anatomical Locations	Bony voids or gaps of the skeletal system, i.e., the extremities, spine and pelvis	Bony voids or gaps of the skeletal system, i.e., the extremities, spine and pelvis	Bony voids or gaps of the skeletal system, i.e., the extremities, spine and pelvis
Labeling	Labeling contains same intended use as predicate devices	Labeling contains same intended use as *Vitoss Scaffold*	Labeling contains same intended use as *Vitoss Scaffold*
Materials	β-Tricalcium Phosphate $Ca_3(PO_4)_2$ satisfies ASTM F 1088	Tricalcium Phosphate – satisfies ASTM F 1088	β-Tricalcium Phosphate $Ca_3(PO_4)_2$ satisfies ASTM F 1088
Design			
• **Physical Structure**	Trabecular structure similar to cancellous bone	Trabecular structure similar to cancellous bone	Uniform, three-dimensional pore structure
• **Porosity**	Approximately 90%	Reported as "highly porous"	Approximately 60% to 70%
• **Pore Size (range)**	1-1000μm		100-500μm
Performance			
• **Osteoconductivity**	Osteoconductive	Osteoconductive	Osteoconductive
• **Resorption**	Demonstrated as 80% resorbed at twelve weeks	Reported as "resorbable"	Resorption reported to occur between 6 and 12 months.
• **Mechanical Strength**	Does not impart mechanical strength to surgical site	Does not impart mechanical strength to surgical site	Does not impart mechanical strength to surgical site
Sterility	Sterilized by gamma radiation, single use only	Sterilized by gamma radiation, single use only	Sterilized by gamma radiation, single use only
Biocompatibility	Established	Established	Established
Dosage Form(s)	Morsels and Blocks	Granules and Blocks	Granules, Cylinders and Blocks

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

AUG 2 9 2003

Ms. Andreina Ide
Sr. Director, Regulatory Affairs
Orthovita, Inc.
45 Great Valley Parkway
Malvern, PA 19355

Re: K032409
Trade Name: Vitoss Scaffold Synthetic Cancellous Bone Void Filler
Regulation Number: 21 CFR 888.3045
Regulation Name: Resorbable calcium salt bone void filler device
Regulatory Class: Class II
Product Code: MQV
Dated: August 1, 2003
Received: August 4, 2003

Dear Ms. Ide:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of Compliance at (301) 594-4659. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address http://www.fda.gov/cdrh/dsma/dsmamain.html

Sincerely yours,

for Mark N Melkerson

Celia M. Witten, Ph.D., M.D.
Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

INDICATIONS FOR USE STATEMENT

510(k) Number: K032409

Device Name: *Vitoss® Scaffold* Synthetic Cancellous Bone Void Filler

Indications For Use:

Vitoss Scaffold Synthetic Cancellous Bone Void Filler is intended for use as a bone void filler for voids or gaps that are not intrinsic to the stability of the bony structure. *Vitoss* Scaffold is indicated for use in the treatment of surgically created osseous defects or osseous defects created from traumatic injury to the bone. *Vitoss* Scaffold should not be used to treat large defects that in the surgeon's opinion would fail to heal spontaneously.

Vitoss Scaffold is intended to be packed into bony voids or gaps of the skeletal system (i.e., the extremities, spine and pelvis) and may be combined with autogenous blood and/or bone marrow. Following placement in the bony void or gap, the calcium phosphate scaffold resorbs and is replaced with bone during the healing process.

PLEASE DO NOT WRITE BELOW THIS LINE
CONTINUE ON ANOTHER PAGE IF NEEDED

Concurrence of CDRH, Office of Device Evaluation (ODE)

for Mark N. Milleman

(Division Sign-Off)
Division of General, Restorative
and Neurological Devices

510(k) Number K032409

Prescription Use _____ OR **Over-The-Counter Use** _____
(Per 21 CFR 801.109)

12

PACKAGE INSERT

GEM 21S®
Growth-factor Enhanced Matrix

Caution: Federal Law restricts this device to sale by or on the order of a dentist or physician.

DEVICE DESCRIPTION:

GEM 21S® is a completely synthetic grafting system for bone and periodontal regeneration composed of a purified recombinant growth factor and a synthetic calcium phosphate matrix.

GEM 21S® is composed of two sterile components:

- synthetic beta-tricalcium phosphate (ß-TCP) [$Ca_3(PO_4)$] is a highly porous, resorbable osteoconductive scaffold or matrix that provides a framework for bone ingrowth, aids in preventing the collapse of the soft tissues and promotes stabilization of the blood clot. Pore diameters of the scaffold are specifically designed for bone ingrowth and range from 1 to 500 µm. The particle size ranges from 0.25 to 1.0 mm and

- highly purified, recombinant human platelet-derived growth factor-BB (rhPDGF-BB). PDGF is a native protein constituent of blood platelets. It is a tissue growth factor that is released at sites of injury during blood clotting. Extensive *in vitro* and animal studies have demonstrated its potent mitogenic (proliferative) and chemotactic (directed cell migration) effects on bone and periodontal ligament derived cells. Animal studies have shown PDGF to promote the regeneration of periodontal tissues including bone, cementum, and periodontal ligament (PDL).

The contents of the cup of ß-TCP are supplied sterile by gamma irradiation. Sterile rhPDGF-BB is aseptically processed and filled into the syringe in which it is supplied.

INDICATIONS:

GEM 21S® is indicated to treat the following periodontally related defects:

- Intrabony periodontal defects;
- Furcation periodontal defects; and
- Gingival recession associated with periodontal defects.

CONTRAINDICATIONS:

As with any periodontal procedure where bone grafting material is used, *GEM 21S®* is CONTRAINDICATED in the presence of one or more of the following clinical situations:

- Untreated acute infections at the surgical site;
- Untreated malignant neoplasm(s) at the surgical site;
- Patients with a known hypersensitivity to any product component (ß-TCP or rhPDGF-BB);
- Intraoperative soft tissue coverage is required for a given surgical procedure but such coverage is not possible; or
- Conditions in which general bone grafting is not advisable.

PACKAGE INSERT

GEM 21S®
Growth-factor Enhanced Matrix

WARNINGS:

The exterior of the cup and syringe are NOT sterile. See directions for use.
It is not known if *GEM 21S®* interacts with other medications. The use of *GEM 21S®* with other drugs has not been studied. Carcinogenesis and reproductive toxicity studies have not been conducted.

The safety and effectiveness of *GEM 21S®* has not been established:

- In other non-periodontal bony locations, including other tissues of the oral and craniofacial region such as bone graft sites, tooth extraction sites, bone cavities after cystectomy, and bone defects resulting from traumatic or pathological origin. GEM 21S® has also not been studied in situations where it would be augmenting autogenous bone and other bone grafting materials.
- In pregnant and nursing women. It is not known whether rhPDGF-BB is excreted in the milk of nursing women.
- In pediatric patients below the age of 18 years.
- In patients with teeth exhibiting mobility of greater than Grade II or a Class III furcation.
- In patients with frequent or excessive use of tobacco products.

Careful consideration should be given to alternative therapies prior to performing bone grafting in patients:

- Who have severe endocrine-induced bone diseases (*e.g.* hyperparathyroidism);
- Who are receiving immunosuppressive therapy; or
- Who have known conditions that may lead to bleeding complications (*e.g. hemophilia*).

The *GEM 21S®* grafting material is intended to be placed into periodontally related defects. It must not be injected systemically.

The radiopacity of *GEM 21S®* is comparable to that of bone and diminishes as *GEM 21S®* is resorbed. The radiopacity of *GEM 21S®* must be considered when evaluating radiographs as it may mask underlying pathological conditions.

PRECAUTIONS:

GEM 21S® is intended for use by clinicians familiar with periodontal surgical grafting techniques.
GEM 21S® is supplied in a single use kit. Any unopened unused material must be discarded and components of this system should not be used separately.

PACKAGE INSERT

GEM 21S®
Growth-factor Enhanced Matrix

HOW *GEM 21S®* IS SUPPLIED:

Each *GEM 21S®* kit consists of:

(1) one cup containing 0.5 cc of ß-TCP particles (0.25 to 1.0 mm); and

(2) one syringe containing a solution of 0.5 ml rhPDGF-BB (0.3 mg/ml).

All of these components/accessories are **for single use only.**

CLINICAL STUDY:

A 180 patient, double-blinded, controlled, prospective, randomized, parallel designed multicenter clinical trial in subjects who required surgical intervention to treat intraosseous periodontal defects was completed.

The major inclusion criteria were:

a. No localized aggressive periodontitis
b. Treatment site with the following characteristics:
   - Probing pocket depth ≥ 7mm at baseline,
   - After surgical debridement, ≥ 4mm vertical bone defect with at least 1 bony wall,
   - Sufficient keratinized tissue to allow complete tissue coverage of defect, and
   - Radiographic base of defect ≥ 3mm coronal to the apex of the tooth.

The major exclusion criteria were:

a. No periodontal surgery on the subject tooth within the last year.
b. No significant recent tobacco use.
c. Allergy to yeast-derived products.
d. Using an investigational therapy within the past 30 days.

The duration of the study was six (6) months following implantation of the product. Patients were randomized into three patient treatment groups:

- Group I (n=60): ß-TCP and 0.3 mg/ml rhPDGF-BB (*GEM 21S®*)
- Group II (n=61): ß-TCP and 1.0 mg/ml rhPDGF-BB
- Group III (n=59): ß-TCP and buffer alone (active control)

The baseline characteristics among the subjects in each group were similar with the exception of "base of defect to root apex". Group I had a mean defect which was significantly less than in Group III (6.5mm vs. 7.7mm, p=0.04).

Schedule of Patient Visits

Patients had 4 visits over the 6 months prior to surgery and device implantation. Scaling and root planing were performed if necessary within 3 months prior to the implant surgery date (Visit 5). Following implantation, subjects underwent 4 follow-up visits during the

first 24 days to assess wound healing and pain assessment and then 4 further follow-up visits every 6 weeks through 6 months. At these latter visits, clinical measurements and radiographs were performed.

Endpoints
The pre-defined primary effectiveness endpoint was the mean change in CAL between baseline and 6 months. Results were to be compared 1) for each group to a historically established level of effectiveness (mean change of 1.5 mm) and 2) between Group I and Group III. The pre-defined secondary endpoints included:

- Comparison of linear bone growth (LBG)
- Comparison of % bone defect fill (%BF) based on radiographs
- Area under the curve for change in CAL
- Change in CAL between baseline and 6 months
- Pocket depth reduction (PDR) change between baseline and 6 months
- Gingival recession (GR) change between baseline and 6 months
- Wound healing during first 3 weeks post-operatively

Primary Endpoint Results
The primary effectiveness endpoint was evaluated using the mean change in CAL gain (mm) from baseline to 6 months for each of the three groups. Mean changes at 6 months are presented in the Table below:

Group of Interest and Change	Control Group and Change	Difference	p-value
Group I 3.7 mm	Historical 1.5 mm	2.2 mm	***<0.001***
Group II 3.7 mm	Historical 1.5 mm	2.2 mm	***<0.001***
Group III 3.5 mm	Historical 1.5 mm	2.0 mm	***<0.001***
Group I 3.7 mm	Group III 3.5 mm	0.2 mm	0.20

As seen in the table above, all three groups, including the control group, had statistically and clinically meaningful mean CAL gains when compared to the historically established 1.5 mm level ($p<0.001$). At 6 months, there was no statistically or clinically significant difference in CAL gain for the low-concentration group (Group I) when compared to the active control without GEM 21S® ($p=0.20$). However, at 3 months (not included in the Table above), the difference was 0.5 mm (3.8 mm vs 3.3 mm) which was statistically significant ($p=0.04$) suggesting that the device may facilitate *earlier* resolution of periodontal intrabony lesions.

Secondary Endpoint Results

As noted above, numerous secondary endpoints were pre-defined in the clinical protocol. The results for these are presented in the Table below. The results represent changes from baseline to 6 months unless otherwise noted.

Parameter	Primary Group and Mean Change	Control Group and Mean Change	Difference in Means	p-value
Linear Bone Growth	Group I 2.52 mm	Group III 0.89 mm	1.63 mm	***<0.001***
	Group II 1.53 mm	Group III 0.89 mm	0.64 mm	***0.02***
% Bone Fill	Group I 56.0%	Group III 17.9%	38.1%	***<0.001***
	Group II 33.9%	Group III 17.9%	16.0%	***0.02***
AUC for CAL Gain (mm-weeks)	Group I 67.5	Group III 60.1	7.4	***0.05***
	Group II 61.8	Group III 60.1	1.7	0.35
CAL Gain	Group II 3.7 mm	Group III 3.5 mm	0.2 mm	0.29
PDR	Group I 4.4mm	Group III 4.2 mm	0.2 mm	0.38
	Group II 4.3 mm	Group III 4.2 mm	0.1 mm	0.66
PDR – 3 Months*	Group I 4.2 mm	Group III 4.2 mm	0.0 mm	0.80
	Group II 4.1 mm	Group III 4.2 mm	0.1 mm	0.67
GR	Group I 0.7 mm	Group III 0.7 mm	0.0 mm	0.95
	Group II 0.6 mm	Group III 0.7 mm	0.1 mm	0.81
GR – 3 Months*	Group I 0.5 mm	Group III 0.9 mm	0.4 mm	***0.04***
	Group II 0.7 mm	Group III 0.9 mm	0.2 mm	0.46

* Not a pre-defined secondary or primary endpoint.

The table illustrates that both the low- and high-dose device achieved significant improvement over the control device (no rhPDGF-BB) at 6 months for linear bone growth and percent bone fill. Although other parameters (CAL gain and gingival recession) showed significant changes at 3 months for the high-dose group, these benefits were not maintained

over control at 6 months. Again, several of these results suggest that the device facilitates *earlier* resolution of periodontal intrabony lesions.

Safety
There were 18 patients (7 Group I, 6 Group II, 5 Group III) with adverse events reported as related to the device. None of these were serious. They were all classified as surgical site reactions. There were no significant differences in the incidence of adverse events across the three treatment groups.

Conclusion
GEM 21S® was shown, by both clinical and radiographic measures, to be effective in treating moderate to severe periodontally related defects within six months of implantation. When implanted into bony defects of the periodontium, *GEM 21S®* has been shown to speed clinical attachment level (CAL) gain, reduce gingival recession, and improve bone growth resulting in increased bone fill of the osseous defect.

ADVERSE EVENTS:

Although no serious adverse reactions attributable to *GEM 21S®* were reported in a 180 patient clinical trial, patients being treated with *GEM 21S®* may experience any of the following adverse events that have been reported in the literature with regard to periodontal surgical grafting procedures: swelling; pain; bleeding; hematoma; dizziness; fainting; difficulty breathing, eating, or speaking; sinusitis; headaches; increased tooth mobility; superficial or deep wound infection; cellulitis; wound dehiscence; neuralgia and loss of sensation locally and peripherally; and, anaphylaxis.

Occurrence of one or more of these conditions may require an additional surgical procedure and may also require removal of the grafting material.

DIRECTIONS FOR USE:

ASEPTIC TECHNIQUE

- The contents of the cup of ß-TCP are supplied sterile by gamma radiation.
- Sterile rhPDGF-BB is aseptically processed and filled into the syringe in which it is supplied.

The exterior portion of the cup of ß-TCP and the exterior surface of the syringe are non-sterile. Because of this, it is recommended that transfer of the ß-TCP particles to a sterile container in the sterile operating field be performed in a sterile manner prior to adding the PDGF from the syringe. Care must also be taken to minimize crushing the ß-TCP particles. Appropriate sterile transfer techniques must be used to prevent contamination of the contents of the cup and syringe.

SURGICAL TECHNIQUE

Familiarization with the device and following proper surgical grafting techniques are extremely important when using *GEM 21S®*. Radiographic evaluation of the defect site

prior to use is essential to accurately assess the extent of the defect and to aid in the placement of the grafting material.

Following exposure of the defect with a full thickness mucoperiosteal flap, all granulation tissue must be carefully removed. Thorough soft tissue debridement of the defect is critical to successful regeneration. Granulation tissue, if left in the defect, could be stimulated by the rhPDGF-BB component, diminishing the desired regenerative response. Exposed tooth root surfaces should also be thoroughly planed.

Following thorough debridement of the osseous defect, the clinician, based on his or her experience, estimates the amount of *GEM 21S®* needed to fill the defect. For best results, *GEM 21S®* must completely fill the defect to the level of the surrounding bony walls. Overfilling should be avoided. The clinician prepares the *GEM 21S®* graft by fully saturating the ß-TCP particles with the rhPDGF-BB solution and letting the product sit for approximately ten (10) minutes. Proper aseptic technique must employed in preparing and applying *GEM 21S®*.

The saturated *GEM 21S®* should be placed into the defect using moderate pressure, taking care not to crush the particles. In order to enhance the formation of new bone, *GEM 21S®* should be placed in direct contact with well-vascularized bone. Excessive bleeding should be controlled prior to placing grafting materials. Following placement of the *GEM 21S®* and completion of any additional surgical steps, the mucoperiosteal flaps should be sutured to achieve primary closure wherever possible.

Postoperative patient management should follow the same regimen as similar cases utilizing autogenous bone grafting. Pre-requisites for all regenerative procedures include prevention of wound dehiscence, a stable clot and minimal bacterial contamination.

The *GEM 21S®* kit and its components must not be re-sterilized by any method or reused. Inspect each individual sterile component of the kit for structural integrity prior to use. If the seal of any inner or outer container is open, broken or otherwise damaged, the product must be assumed to be non-sterile and consequently, must not be used.

Any opened unused material must be discarded and components of this system should not be used separately.

STORAGE CONDITIONS:

The *GEM 21S®* kit must be refrigerated at 2°-8° C (36°-46° F). Do not freeze. The individual rhPDGF-BB component must be refrigerated at 2°-8° C (36°-46° F). The ß-TCP cup can be stored at room temperature, up to 30° C (86° F). The rhPDGF-BB component must be protected from light prior to use; do not remove from outer covering prior to use.

Do not use after the expiration date.

PACKAGE INSERT

GEM 21S®
Growth-factor Enhanced Matrix

BIOCOMPATIBILITY:
GEM 21S® biocompatibility has been demonstrated in accordance with the International Standard ISO 10993-1:1997 "Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing."

Manufactured By:

BioMimetic Therapeutics, Inc.
389-A Nichol Mill Lane
Franklin, TN 37067

Distributed By:

Osteohealth Company
Division of Luitpold Pharmaceuticals, Inc.
One Luitpold Drive
PO Box 9001
Shirley, NY 11967
(800) 874-2334

This product is sold and distributed under US patents:
4,845,075
5,045,633
5,124,316

November 18, 2005

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BIOMIMETIC GEM 21 S PRODUCT - FDA CHRONOLOGY

Date	*Activity*
13-Dec-01	BMTI original submission of IDE submission
11-Jan-02	Original IDE submission deficiencies identified by FDA
15-Jan-02	BMTI responded to FDA's January 6, 2003 telephone inquiry for additional information on Interim Analysis
31-Jan-02	BMTI response to FDA's January 11, 2002 deficiencies
28-Feb-02	FDA conditionally approved IDE
18-Mar-02	BMTI response to FDA's February 28, 2002 conditional approval revising the pivotal study protocol to include an interim analysis
24-Apr-02	FDA approves BMTI's response to FDA's February 28, 2002 conditional approval
17-Jul-02	Notification of the IRB approval
24-Sep-02	BMTI submits Interim Analysis Protocol (statistical plan)
26-Sep-02	FDA does not approve revisions to the Statistical Analysis Plan
10-Oct-02	FDA approves (via phone) Interim Analysis Protocol (statistical plan)
03-Dec-02	BMTI submitted results of the November 18, 2002 interim statistical analysis
Week of 6-Jan-03	FDA requested (via phone) additional details regarding interim statistical analysis
17-Feb-03	FDA approves (via phone) BMTI response to FDA's January 6, 2003 telephone inquiry for additional information on Interim Analysis
05-May-03	BMTI submitted a revision copy of the statistical analysis plan to change concentration of PDGF to 0.3mg/ml
09-May-03	FDA approves revision copy of the statistical analysis plan to change concentration of PDGF to 0.3mg/ml
29-Jul-03	BMTI submitted annual report in accordance with 21 CRF 812.150(b)(5)
25-Aug-03	FDA approves (via phone) annual report submitted in accordance with 21 CRF 812.150(b)(5)
27-Aug-03	BMTI submitted a revision to the Statistical Analysis Plan
11-Sep-03	BMTI submitted changes to August 27, 2003 Statistical Analysis Plan
24-Oct-03	BMTI submitted response to FDA's September 26 explanation of deficiencies regarding revisions to the Statistical Analysis Plan
25-Nov-03	FDA approves revisions to Statistical Analysis Plan
24-Dec-03	BMTI submitted Pre-PMA filing meeting and a draft of the Clinical Study Report.
29-Dec-03	FDA requested additional details (via telephone call) regarding submitted Pre-PMA filing meeting and draft of the Clinical Study Report
28-Jan-04	FDA approved Pre-PMA filing meeting and a draft of the Clinical Study Report.
28-Jan-04	FDA acknowledges and closes completion of IDE
09-Feb-04	Minutes of February 3, 2003 Pre-PMA filing review
09-Feb-04	BMTI submits Pre-PMA Meeting Minutes

Date	Activity
10-Feb-04	FDA receipt of Pre-PMA Meeting Minutes
12-Mar-04	PMA Submission Original Acknowledgement Receipt
24-Mar-04	PMA Revision; Typographical Errors
25-Mar-04	FDA receives PMA Revision
09-Apr-04	Transmittal Letter, Updated SS&E w/ PDF
14-Apr-04	CBER Response to PDGF RE: Purity, Potency, and Consistency of PDGF
16-Apr-04	FDA accepts PMA for filing
26-Apr-04	FDA schedules dental products panel of the Medical Devices Advisory Committee Meeting for July 13, 2004
19-May-04	FD 482 Notice for BIMO Audit at BMTI
02-Jun-04	Teleconference call minutes; additional information on b-TCP
03-Jun-04	BMTI submits Table of Contents 5 Volume Non-Public Release Sponsors' Panel Package
04-Jun-04	BMTI submits Table of Contents 2 Volume Public Panel Package
04-Jun-04	FDA receives Table of Contents 5 Volume Non-Public Release Sponsors' Panel Package
05-Jun-04	FDA receives Table of Contents 2 Volume Public Panel Package
23-Jun-04	FDA 483 from Kristin S. Tharp of the FDA to Dr. Thomas Hahn, DDS.
29-Jun-04	BMTI responded on behalf of Dr. Hahn to FDA 483 from KS Tharp.
02-Jul-04	BMTI updated letter of cross-reference to Orthovita
02-Jul-04	BMTI submitted response to FDA request for supplementary Statistical Analyses
07-Jul-04	FDA received updated letter of cross-reference to Orthovita
07-Jul-04	FDA received BMTI rsponse to FDA request for supplementary Statistical Analyses
08-Jul-04	BMTI submitted Manufacturing Validation Reports
16-Jul-04	MAF-1294 Orthovita; Notification of cross-reference
23-Jul-04	Transmittal of Panel Information
26-Jul-04	IDE vs. Commercial Manufacturing
27-Jul-04	BMTI submitted Bioassay Report in reference to amendment A005
27-Jul-04	BMTI submitted Kendall Healthcare Reference Information via Fax
28-Jul-04	FDA received Bioassay Report in reference to amendment A005
30-Jul-04	BMTI emailed FDA responding to telephone inquiry on comparison's between IDE stage and PMA stage
03-Aug-04	BMTI submitted to FDA amendment comparing PDGF component clinical vs. commercial to show that there was not change from the IDE submission to the PMA
04-Aug-04	FDA acknowledge receipt of BMTI August 3, 2004 amendment
05-Aug-04	BMTI submitted reference to A006, electronic copy (PDF) of PMA Amendment to Dr. Stromberg
05-Aug-04	BMTI submitted reference to A006, electronic copy (PDF) of PMA Amendment to Angela Blackwell

Date	Activity
12-Aug-04	Compliance Deficiency Letter on Cannula; Insufficient Information regarding Amendment A005
25-Aug-04	BMTI submitted amendment to FDA addressing question the FDA had on Kendall Healthcare cannula being used in GEM 21S kit
31-Aug-04	BMTI submitted to FDA and amendment comparing β-TCP IDE vs. PMA (Clinical vs. Commercial)
03-Sep-04	FDA acknowledge receipt of BMTI August 31, 2004 amendment
09-Sep-04	The Agency Acknowledged response in a September 9, 2004 letter to Dr. Hahn
14-Sep-04	FDA acknowledge receipt of BMTI August 25, 2004 amendment
21-Sep-04	BMTI's Letter of Reference to Osteohealth for IDE
22-Sep-04	FDA receives BMTI's Letter of Reference to Osteohealth for IDE
29-Sep-04	Deficiency Letter from the FDA on Amendments A001-A009
06-Oct-04	BMTI acknowledgement of September 29, 2004 Letter from FDA
07-Oct-04	FDA receives BMTI acknowledgement of September 29, 2004 Letter
08-Oct-04	BMTI submits Label, Insert, & SS&E
12-Oct-04	BMTI submits electronic version of SS&E, Label
12-Oct-04	FDA receives Label, Insert, & SS&E
13-Oct-04	FDA receives electronic version of SS&E, Label
22-Oct-04	BMTI response to September 29, 2004 Letter (Analytical Method Validation Report - GEM 21S™ Bioassay Validation Summary)
27-Oct-04	BMTI response to September 29, 2004 Letter (Analytical Report - Validation of Biochemical Analytical Techniques used for the Characterization of rhPDGF-BB)
28-Oct-04	FDA receives BMTI response to September 29, 2004 Letter (Analytical Method Validation Report - GEM 21S™ Bioassay Validation Summary)
28-Oct-04	FDA receives BMTI response to September 29, 2004 Letter (Analytical Report - Validation of Biochemical Analytical Techniques used for the Characterization of rhPDGF-BB)
01-Nov-04	BMTI response to September 29, 2004 Letter (Validation Summary Report - Validation Summary Report for the Sterility Validation for the B-TCP 0.5cc Small Perio Cup)
03-Nov-04	FDA receives BMTI response to September 29, 2004 Letter (Validation Summary Report - Validation Summary Report for the Sterility Validation for the B-TCP 0.5cc Small Perio Cup)
05-Nov-04	Electronic PDF copy of PMA Amendments A016 & A017 to Dr. Stromberg
05-Nov-04	E-mail correspondence with Keisha Thomas and Vertleen Covington to schedule a compliance audit for PMA 040013.
05-Nov-04	E-mail correspondence with Angela Blackwell showing time frames of Amendment submissions 15, 16 & 17
10-Nov-04	E-mail correspondence with Angela Blackwell; attached a revised copy of the SS&E and Package Insert per her request

Date	Activity
24-Dec-04	Follow-up to December 13, 2004 conference call.
27-Jan-05	Fax response from Angela Blackwell to BMTI's October 28, 2004 response to major deficiencies indicating inadequacies.
01-Feb-05	BMTI response to January 27, 2005 Agency Telephone Inquiry [Supplementary Manufacturing Information on Packaging Validation (Shipping & Distribution)]
02-Feb-05	E-mail correspondence with Thinh Nguyen of the FDA; attached a copy of the August 2004 Kendall Healthcare Reference Information
03-Feb-05	BMTI submits response to January 27, 2005 Agency Telephone Inquiry (Audit Contacts)
03-Feb-05	BMTI response to January 27, 2005 Agency Telephone Inquiry [Supplementary Manufacturing Information on Sterility Validation for GEM 21S™ rhPDGF-BB]
03-Feb-05	FDA receives BMTI response to January 27, 2005 Agency Telephone Inquiry [Supplementary Manufacturing Information on Packaging Validation (Shipping & Distribution)]
04-Feb-05	Dr. Stromberg requesting RP-HPLC assay data via e-mail on stability and transport validation. Dr. Hart responded indicating near completion on this information.
04-Feb-05	FDA receives BMTI response to January 27, 2005 Agency Telephone Inquiry (Audit Contacts)
04-Feb-05	FDA receives BMTI response to January 27, 2005 Agency Telephone Inquiry [Supplementary Manufacturing Information on Sterility Validation for GEM 21S™ rhPDGF-BB]
09-Feb-05	BMTI submits electronic PDF copy of PMA Amendments A018, A019 & A020 to Angela Blackwell
11-Feb-05	BMTI submits response to February 11, 2005 telephone Inquiry (Cannula Sterilization and shipping Information)
11-Feb-05	BMTI submits electronic PDF copy of PMA Amendment A022 to Angela Blackwell
14-Feb-05	FDA receives response to February 11, 2005 telephone Inquiry (Cannula Sterilization and shipping Information)
15-Feb-05	BMTI submits response to February 15, 2005 Agency E-mail (Kurt Stromberg) [Missing page from PMA Amendment A020 (Shipping of rhPDGF-BB Filled Syringes manufacturing report)]
15-Feb-05	BMTI submits response to February 15, 2005 Agency E-mail (Kurt Stromberg) [Shipment of Product SOP (ref. MFP003)]
15-Feb-05	Dr. Hart e-mailed Dr. Stromberg a copy of the validation report in response to question No. 9 of the January 27, 2005 letter
15-Feb-05	E-mail Correspondence from Kurt Stromberg requesting Shipping Request SOP (MFP003) and missing page from PMA Amendment A020

Date	Activity
16-Feb-05	Dr. Hart e-mailed Dr. Stromberg a copy of Bioassay Transfer Summary (att. 7) in response to question No. 1 of the January 27, 2005 letter.
16-Feb-05	BMTI submits Electronic PDF copy of PMA Amendment A022 & A023 to Angela Blackwell
16-Feb-05	BMTI submits electronic PDF copy of PMA Amendment A023 & A024 to Dr. Kurt Stromberg
16-Feb-05	FDA receives BMTI's response to February 15, 2005 Agency E-mail (Kurt Stromberg) [Missing page from PMA Amendment A020 (Shipping of rhPDGF-BB Filled Syringes manufacturing report)]
16-Feb-05	FDA receives BMTI's response to February 15, 2005 Agency E-mail (Kurt Stromberg) [Shipment of Product SOP (ref. MFP003)]
28-Feb-05	BMTI submits E-mail response to Dr. Kurt Stromberg regarding comments made by Agency on January 27, 2005 fax to BMTI (refer to Appendix 40 above)
01-Mar-05	BMTI submits Canine Study Audit Report submitted to Linda Sacco of NY District Division
01-Mar-05	BMTI submits Response to FDA inquiry on traceability of rhPDGF-BB conformance lots
02-Mar-05	BMTI submits response to FDA inquiry on SDS-PAGE; rhPDGF-BB conformance lots
02-Mar-05	BMTI sends correspondence to Susan Runner of the FDA on the March 1, 2005 Canine Study Audit Report that was submitted to Linda Sacco (refer to Appendix 54)
02-Mar-05	FDA receives BMTI's response to FDA inquiry on traceability of rhPDGF-BB conformance lots
02-Mar-05	Faxed agenda from Angela Blackwell for the March 3, 2005 Teleconference regarding timetables from January 27, 2005 fax (see Exhibit 40), etc.
03-Mar-05	FDA requested an electronic copy of the July 8, 2004 PMA submission
03-Mar-05	Electronic PDF copy of sections 6.21.1.15.34 – 6.21.1.15.38 and Attachment 6.21.15.7.21 of PMA Amendment A005 to Angela Blackwell
03-Mar-05	March 3, 2005 Draft minutes of telephone conference between BMTI and FDA on timetables, sterilization issues, packaging issues.
03-Mar-05	FDA receives BMTI response to FDA inquiry on SDS-PAGE; rhPDGF-BB conformance lots
04-Mar-05	BMTI provided additional information regarding stability data
04-Mar-05	Electronic PDF copy of PMA Amendment A024 to Angela Blackwell
04-Mar-05	Electronic PDF copy of PMA Amendment A024 to Dr. Kurt Stromberg
04-Mar-05	Notification to the Mary Jo Robinson of the Agency that Amendment A018 was assigned twice and needed correction.
04-Mar-05	Tyco responding directly to the agency with the Kendall Blunt Needle resubmission

Date	Activity
04-Mar-05	FDA acknowledged receipt of electronic copy of July 8, 2004 submission regarding stability data and requested additional information regarding stability data
05-Mar-05	FDA left voice message requesting information on rpHPLC validation
07-Mar-05	BMTI provided additional information regarding stability data
07-Mar-05	BMTI submits Response to FDA's inquiry on Canine Study. Originally submitted to Linda Sacco on March 1, 2005
07-Mar-05	FDA requested that stability data be submitted as one complete package
08-Mar-05	FDA receives BMTI March 7 response to FDA's inquiry on Canine Study.
08-Mar-05	Dr. Stromberg requesting, via e-mail, a 14 item response from BMTI regarding the January 26, 2005 letter
09-Mar-05	Dr. Hart responding, via e-mail, to the Dr. Strombergs voice-mail requesting information on rpHPLC validation.
09-Mar-05	Angela Blackwell responded (via telephone acknowledging that Amendment A018 was assigned twice and needed correction.
09-Mar-05	BMTI respondedg, via e-mail, to FDA voice-mail requesting information on rpHPLC validation.
11-Mar-05	BMTI follow-up to the March 5, 2005 telephone call to include an attachment of the handling of rhPDGF-BB.
14-Mar-05	Patheon directly submitted information to the Agency on Autoclave Sterilization Validation for rhPDGF-BB Component
15-Mar-05	BMTI telephone call with Dr. Stromberg on Arg32 levels and rationale for 24 month expiry date
17-Mar-05	Dr. Hart follow-up to the February e-mail sent to Dr. Stromberg per his request. Dr. Hart included the e-mail along with the bioassay data table for stability samples.
17-Mar-05	Angela Blackwell requesting additional info on the Cannula.
18-Mar-05	BMTI reply to Angela Blackwell request for additional info on the Cannula.
18-Mar-05	Mark Citron e-mailed A. Blackwell a draft copy of the GEM 21S Package Performance Test; supplementary Sterility Test
18-Mar-05	FDA receives Patheon information on Autoclave Sterilization Validation for rhPDGF-BB Component
21-Mar-05	FDA requested summarization of BMTI's changes in response to February 28, 2005 correspondence to FDA
21-Mar-05	BMTI sent e-mail to Thinh Nguyen of FDA to acknowledge Sterilization Validation information for the autoclaves at Patheon requested by Bob Riley will be part of PMA filing
21-Mar-05	BMTI responded to FDA request for summarization of BMTI's changes in response to February 28, 2005 correspondence to FDA

Date	Activity
22-Mar-05	BMTI notified Dr. Stromberg, via e-mail, of the proposed latest changes to the response letter to the January 27, and February 15, 2005 agency e-mails relating to SDS page and bioassay issue.
22-Mar-05	BMTI follow-up, via e-mail, with Angela Blackwell regarding verification of amendment numbers
23-Mar-05	Correspondence from BMTI to FDA regarding SDS page and bioassay issue.
24-Mar-05	Tyco responding directly to the agency with additional Kendall Blunt Needle information
24-Mar-05	BMTI e-mailed Dr. Stromberg as a follow-up to the March 23, 2005 telephone call. Jim provided Dr. Stromberg a table outlining historical correspondence between BMTI and the Agency
24-Mar-05	BMTI submits response to FDA inquires from January 27, 2005 e-mail and other correspondence
25-Mar-05	FDA receives Tyco responds to the agency regarding additional Kendall Blunt Needle information
28-Mar-05	Jim Monsor e-mailed Joan Loreng of FDA on Audit schedule in UK. Amendment 31
30-Mar-05	Correspondence from FDA to BMTI regarding SDS page and bioassay issue.
30-Mar-05	Correspondence from FDA to BMTI regarding SDS page and bioassay issue.
30-Mar-05	Joan Loreng of FDA requested volumes 4 & 5 of Amendment 31
01-Apr-05	BMTI submits package insert correction from March 24, 2005 submission (see A030). Also submitted revised kit labeling showing that the cannula was removed
04-Apr-05	Electronic PDF copy of PMA Amendment A030 sent to Joan Loreng of FDA.
04-Apr-05	Electronic PDF copy of PMA Amendment A031 sent to A. Blackwell of FDA.
04-Apr-05	FDA receives package insert correction from March 24, 2005 submission (see A030) and revised kit labeling showing that the cannula was removed
07-Apr-05	Electronic PDF copy of PMA Amendment A005 (Volumes 5(a),(b),(c) and 6(a),(b) sent to Joan Loreng of FDA.
07-Apr-05	E-mail to Joan Loreng from Jim Monsor to confirm receipt of information requested for UK audits.
07-Apr-05	BMTI PMA follow-up commitments to Kurt Stromberg via e-mail from Jim Monsor.
11-Apr-05	Confirmation of audit dates for FDA inspection at BMTI facility and driving directions
13-Apr-05	BMTI submits Supplementary Stability Information (Use of Reverse Phase HPLC Method as a Stability Indicating Assay)

Date	Activity
13-Apr-05	FDA internal correspondence on PMA review for GEM 21S. Received from Cherie Parker.
14-Apr-05	BMTI submits electronic PDF copy of PMA Amendment A032 sent to Dr. Kurt Stromberg of FDA.
14-Apr-05	BMTI submits electronic PDF copy of PMA Amendment A032 sent to A. Blackwell of FDA.
14-Apr-05	BMTI submits electronic copy of requested QSIT audit documentation from April 13, 2005 FDA Audit.
14-Apr-05	FDA receives Supplementary Stability Information (Use of Reverse Phase HPLC Method as a Stability Indicating Assay)
19-Apr-05	Kurt Stromberg (FDA) inquired of stability and photostability information.
20-Apr-05	Charlie Hart responded to Kurt Stromberg (FDA) inquiry of stability and photostability information.
20-Apr-05	Response letter from FDA to Dr. Robert Genco regarding Feb 22-Mar 4, 2005 audit of University of NY at Buffalo facility
21-Apr-05	BMTI response to April 21, 2005 request from Cherie Parker re: the QSIT audit. Submitted additional information on Amendment 031
21-Apr-05	BMTI response to April 18, 2005 request from Cherie Parker re: QSIT audit. Submitted summary information on rhPDGF-BB sterile fill validations at Patheon.
22-Apr-05	BMTI supplier responded to Form FDA 483 from Joan Loreng of the FDA.
22-Apr-05	Form FDA 483 from Joan A. Loreng of the FDA sent to BMTI supplier.
22-Apr-05	Tyco submitted correct Validation Report on the Kendall Blunt Needle to the Agency
26-Apr-05	FDA receives Tyco correct Validation Report on the Kendall Blunt Needle to the Agency
28-Apr-05	Form FDA 483 from Joan A. Loreng of the FDA to BMTI supplier.
01-May-05	Letter from FDA summarizing inspection results from the February 22 through March 4, 2005 audit of SUNY at Buffalo
04-May-05	Howard Holstein of Hogan & Hartson e-mailed Thinh Nguyen of the FDA to discuss status of PMA
06-May-05	M. Citron e-mailed Thinh Nguyen of the FDA as a follow-up to their May 6, 2005 telephone conversation on additional rhPDGF-BB studies from BMTI supplier
06-May-05	FDA contact report on Inquiry of PMA A033 from Tom Golden
10-May-05	Kurt Stromberg of the FDA e-mailed Jim Monsor and Charlie Hart inquiring when bioassay and SDS-Page would be submitted to CDER
11-May-05	BMTI responded FDA's inquiry regarding when bioassay and SDS-Page would be submitted to CDER.
13-May-05	Charlie Hart e-mailed Kurt Stromberg of the FDA on follow-up to Kurt's May 10, 2005 e-mail regarding the Bioassay.

Date	Activity
13-May-05	M. Citron e-mailed Thinh Nguyen of the FDA to see if he had spoken with Dr. Runner.
13-May-05	FDA replied to BMTI May 13 email.
17-May-05	BMTI submitted Supplementary Information on rhPDGF-BB Component
17-May-05	Kurt Stromberg e-mailed Charlie Hart inquiring on Photostability Study.
17-May-05	Electronic PDF copy of PMA Amendment A034 sent to Dr. Kurt Stromberg of FDA.
18-May-05	Electronic PDF copy of PMA Amendment A034 sent to A. Blackwell of FDA.
18-May-05	FDA received Supplementary Information of rhPDGF-BB Component
18-May-05	BMTI responded to FDA's inquiry regarding Photostability Study.
19-May-05	Mark Citron e-mailed Thinh Nguyen of the FDA regarding concerns on additional bioassay testing that was requested by Kurt Stromberg
19-May-05	Kurt Stromberg of the FDA e-mailed Mark Citron regarding explanation of bioassay request.
19-May-05	BMTI responded to FDA e-mail of May 19 indicating its main objective on moving forward without further testing.
25-May-05	C. Hart e-mailed Kurt Stromberg on Bioassay data information along with a Draft copy of Statistical Analysis of rhPDGF-BB Mitogenic Bioassay data.
31-May-05	BMTI submitted letter to FDA FOI for copy request of EIR for the State University of New York at Buffalo Audit (2/22-3/4 2005)
31-May-05	BMTI submitted letter to FDA FOI for copy request of EIR for BioMimetic Pharmaceuticals Audits (5/19/04 & 4/13/05)
31-May-05	BMTI submitted letter to FDA FOI for copy request of EIR for Thomas Han Audit (6/9-10, 15, 22-23 2005)
02-Jun-05	FDA acknowledge receipt of BMTI letter to FDA FOI for copy request of EIR for BioMimetic Pharmaceuticals Audits (5/19/04 & 4/13/05)
03-Jun-05	M. Citron confirming June 20th Bioassay conference calls with the FDA. Also verifying that all other issues have been addressed.
06-Jun-05	Charlie Hart e-mailed Judy Chen of the FDA the revised protocol on the GEM 21S bioassay to review
09-Jun-05	C. Hart requesting from Dr. Stromberg of FDA Biostatistician feedback.
09-Jun-05	FDA acknowledge receipt of BMTI letter to FDA FOI for copy request of EIR for the State University of New York at Buffalo Audit (2/22-3/4 2005)
15-Jun-05	M. Citron e-mailed Angela Blackwell inquiring on info for June 22, 2005 teleconference
16-Jun-05	FDA acknowledge receipt of BMTI letter to FDA FOI for copy request of EIR for Thomas Han Audit (6/9-10, 15, 22-23 2005)
22-Jun-05	Status telephone conference with FDA to resolve GEM 21S approval open issues

Date	Activity
24-Jun-05	BMTI emailed FDA acknowledging June 22, 2005 teleconference on progress of GEM 21S Approval.
28-Jun-05	E-mail to Dr. Stromberg of FDA with draft bioassay protocol and report to progress approval for GEM 21S
29-Jun-05	FDA replied to BMTI June 24 email, and requested a copy of GEM 21S labeling
30-Jun-05	Dr. Stromberg of FDA replying to Meeting Minutes from June 22, 2005 teleconference call with additions and changes
30-Jun-05	BMTI responded to FDA June 29 request and provided GEM 21S labeling
06-Jul-05	BMTI e-mailed FDA to address remaining issues to satisfy the Agencies requirements for GEM 21S approval. K. Stromberg responded requesting shipping validation info
12-Jul-05	Mark Citron e-mailed Angela Blackwell and Mary Runner of the FDA on the supplementary information requested by CDER.
12-Jul-05	A. Blackwell requested a word version of the SS&E and Package Insert.
12-Jul-05	A. Blackwell notified M. Citron to inform DMC of BMTI's address change.
13-Jul-05	M. Citron notified A. Blackwell that bioassay statistics came out fine
13-Jul-05	BMTI submitted 18 Month Stability report; rhPDGF-BB Component Amendment
14-Jul-05	BMTI submitted rhPDGF-BB Component; Mitogenic Bioassay Supplementary Data Amendment
14-Jul-05	BMTI Notified PMA Document Mail Center of new address
14-Jul-05	C. Hart faxed K. Stromberg raw data of the BMTI bioassay data
14-Jul-05	FDA received 18 Month Stability report; rhPDGF-BB Component Amendment
15-Jul-05	Electronic PDF copy of PMA Amendment A035 & A036 sent to Dr. Kurt Stromberg of FDA.
15-Jul-05	Electronic PDF copy of PMA Amendment A035 & A036 sent to A. Blackwell of FDA.
15-Jul-05	BMTI submitted study report regarding bioassay to FDA
16-Jul-05	M. Citron (BMTI) followed-up, via e-mail, with Thinh Nguyen of the FDA to relay results of bioassay and to request quick turn-around for GEM 21S approval.
26-Jul-05	BMTI submits Inspection Responses to the FDA from the May 16-20, 2005 audit of BMTI supplier
27-Jul-05	FDA responded to BMTI July 6 email, and requested shipping validation information
28-Jul-05	BMTI submitted to FDA the shipping validation information requested on July 27, 2005
28-Jul-05	Howard Holstein e-mailed M. Kramer and L. Weinstein of the FDA to follow-up from previous discussions and clarify PMA Approval problems

Date	Activity
29-Jul-05	Angela Blackwell emailed BMTI with FDA's edited version of the GEM 21S Package insert.
29-Jul-05	BMTI forwarded Angela Blackwell July 29 emailed to Thin Nguyen
02-Aug-05	BMTI responded to FDA August 2 request, and acknowledged that amendment would take place
02-Aug-05	FDA replied study report submitted on July 15, 2002, and requested to amend an AAI Bioassay.
03-Aug-05	BMTI e-mailed Dr. Runner of FDA as a follow-up to August 2, 2005 conference call. This e-mail was forwarded to Thinh Nguyen as well.
03-Aug-05	BMTI e-mailed Patricia Love of the FDA notifying her of productive 8/2/05 conference with the agency
05-Aug-05	BMTI letter to Dr. Runner of the FDA addressing concerns with FDA's decisions from 8/4/05 teleconference call
08-Aug-05	BMTI submits Bioassay; Method Revision
08-Aug-05	BMTI submits electronic PDF copy of PMA Amendment A038 sent to Dr. Kurt Stromberg of FDA.
08-Aug-05	BMTI submits electronic PDF copy of PMA Amendment A038 sent to A. Blackwell of FDA.
09-Aug-05	BMTI e-mailed Dr. Runner of the FDA thanking her for looking into the issues surrounding the issues that are holding up approval
09-Aug-05	BMTI e-mailed Dr. Stromberg of the FDA regarding the Stability Specification clarification
16-Aug-05	BMTI e-mailed Dr. Runner of the FDA with information on Commercial Inventory for GEM 21S and notifying her that BMTI supplier is available to assist the Agency
17-Aug-05	BMTI sent letter notifying Dr. Susan Runner of CDRH of recent teleconference call with Dr. Love of the Combination Products Division. The letter also granted FDA permission to speak with BMTI supplier on PMA matters related to BioMimetic's GEM 21S
18-Aug-05	BMTI e-mailed Angela Blackwell of the FDA asking her to contact him if she has questions regarding units used in the bioassay
18-Aug-05	BMTI notified Dr. Patricia Love via e-mail that BMTI supplier is waiting to hear from the FDA on potential questions regarding their manufacturing facility.
19-Aug-05	BMTI provided Dr. Stromberg Draft of study procedure on Bioassay results
23-Aug-05	Communication with the FDA regarding request for four recent PMA amendment titles from PMA Center
23-Aug-05	BMTI emailed FDA expressing concerns regarding FDA's request for additional protocol information.
24-Aug-05	Communication with the FDA regarding request for four recent PMA amendment titles from PMA Center

Date	Activity
25-Aug-05	MC forwarded e-mail to Dr. Love and requested further clarification on CDER communication to CDRH
25-Aug-05	Howard Holstein forwarded BMTI's e-mail from August 23 to Les Weinstein and Thinh Nguyen regarding problems with CBER.
26-Aug-05	FDA responded to BMTI email of August 23 and provided clarification
29-Aug-05	BMTI submits revised Package Insert and Summary of Safety and Effectiveness
30-Aug-05	BMTI submits electronic PDF copy of PMA Amendment A041 sent to A. Blackwell of FDA.
30-Aug-05	BMTI e-mailed Dr. Runner with the updated version of the SS&E and Package Insert
01-Sep-05	BMTI e-mailed Dr. Runner as a follow-up to the September 1, 2005 teleconference call on the Package insert.
07-Sep-05	H. Holstein of Hogan & Hartson L.L.P e-mailed Les Weinstein of CDRH inquiring of delay for PMA approval
07-Sep-05	FDA e-mailed BMTI verifying that the September 7th teleconference call would satisfy as the weekly update.
09-Sep-05	BMTI responded to FDA's request, via e-mail, on the lot traceability table from BMTI supplier
10-Sep-05	BMTI e-mailed Tim Ulatowski of FDA asking if there were any concerns since Tim would now have direct involvement of PMA approval process.
12-Sep-05	BMTI responded to Dr. FDA Sept. 7 email and updated Dr. Love and Dr. Runner of BMTI supplier's action on revising the table.
20-Sep-05	BMTI e-mailed Drs. Runenr & Love informing them that BMTI would remove supplier's facility from the PMA
20-Sep-05	A. Blackwell e-mailed BMTI requesting a photo of cup and syringe components
20-Sep-05	BMTI submits revised Specifications; QC Modifications for rhPDGF-BB
20-Sep-05	BMTI-FDA follow-up to telephone call regarding exclusion of BMTI supplier's manufacturing facility
21-Sep-05	BMTI submits electronic PDF copy of PMA Amendment A043 to Dr. Kurt Stromberg of FDA.
21-Sep-05	BMTI submits Electronic PDF copy of PMA Amendment A043 to A. Blackwell of FDA.
21-Sep-05	BMTI sent A. Blackwell a photo of cup and syringe components
22-Sep-05	BMTI responds to Kurt Stromberg via e-mail on agreed language for the SDS Page
23-Sep-05	BMTI submits revised Specifications; rhPDGF-BB Component
23-Sep-05	BMTI submitted a thank you e-mail to Drs. Runner & Love and Donna Tilman of the FDA on the approvable letter.

Date	Activity
23-Sep-05	BMTI submitted a thank you e-mail to A. Blackwell on the approvable letter and attached a copy of the amendment (A044) on the revised specifications.
23-Sep-05	BMTI submitted new SDS language (revised specs) to K. Stromberg and E. Shacter of FDA via e-mail
23-Sep-05	Letter from FDA for PMA P040013 was recommend by the FDA as approvable
23-Sep-05	Angela Blackwell (FDA) notified BMTI of her travels and when she would finish up on the approval package.
28-Sep-05	BMTI forwarded Blackwell (FDA) 9/23 email to Susan Runner (FDA) for further guidance on next steps to approval
28-Sep-05	BMTI submitted electronic PDF copy of PMA Amendment A044 to Dr. Kurt Stromberg of FDA.
28-Sep-05	BMTI submits electronic PDF copy of PMA Amendment A044 to A. Blackwell of FDA.
06-Oct-05	BMTI e-mailed and fed ex copy of the revised release specification as a follow-up to the approvable letter
06-Oct-05	Conference call with FDA regarding additional information in formal letter tying agreement to the conditions of approvaable letter
31-Oct-05	BMTI e-mailed Dr. Tillman of FDA asking for further information to expedite PMA approval process
04-Nov-05	BMTI responded to FDA package insert changes identifying concerns with FDA's changes
04-Nov-05	BMTI e-mailed FDA requesting further clarification as to why the meta-analysis was removed from the Package Insert.
04-Nov-05	Angela Blackwell (FDA) submitted package insert with changes.
07-Nov-05	Angela Blackwell responded to BMTI's inquiries on angiogenesis.
07-Nov-05	BMTI replied to FDA response regarding angiogenesis by providing FDA with scientific references showing that PDGF facilitates angiogenesis.
09-Nov-05	E-mail correspondence with Keisha Thomas and Vertleen Covington to schedule a compliance audit for PMA 040013.

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Delaware

The First State

I, HARRIET SMITH WINDSOR, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THAT THE SAID "BIOMIMETIC PHARMACEUTICALS, INC.", FILED A CERTIFICATE OF AMENDMENT, CHANGING ITS NAME TO "BIOMIMETIC THERAPEUTICS, INC.", THE FIFTH DAY OF AUGUST, A.D. 2005, AT 7:53 O'CLOCK P.M.

AND I DO HEREBY FURTHER CERTIFY THAT THE AFORESAID CORPORATION IS DULY INCORPORATED UNDER THE LAWS OF THE STATE OF DELAWARE AND IS IN GOOD STANDING AND HAS A LEGAL CORPORATE EXISTENCE NOT HAVING BEEN CANCELLED OR DISSOLVED SO FAR AS THE RECORDS OF THIS OFFICE SHOW AND IS DULY AUTHORIZED TO TRANSACT BUSINESS.

Harriet Smith Windsor

Harriet Smith Windsor, Secretary of State

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050657582

AUTHENTICATION: 4081005

DATE: 08-09-05

Delaware

The First State

I, HARRIET SMITH WINDSOR, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF AMENDMENT OF "BIOMIMETIC PHARMACEUTICALS, INC.", CHANGING ITS NAME FROM "BIOMIMETIC PHARMACEUTICALS, INC." TO "BIOMIMETIC THERAPEUTICS, INC.", FILED IN THIS OFFICE ON THE FIFTH DAY OF AUGUST, A.D. 2005, AT 7:53 O'CLOCK P.M.

A FILED COPY OF THIS CERTIFICATE HAS BEEN FORWARDED TO THE KENT COUNTY RECORDER OF DEEDS.

Harriet Smith Windsor

Harriet Smith Windsor, Secretary of State

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050649698

AUTHENTICATION: 4080589

DATE: 08-09-05

CERTIFICATE OF AMENDMENT TO
CERTIFICATE OF INCORPORATION
OF
BIOMIMETIC PHARMACEUTICALS, INC.

BioMimetic Pharmaceuticals, Inc., a corporation organized and existing under the General Corporation Law of the State of Delaware (the "Corporation"), does hereby certify:

FIRST: The Certificate of Incorporation of the Corporation is hereby amended by striking Article I in its entirety and replacing therefor the following:

I.

The name of the corporation (hereinafter called the "Corporation") is BioMimetic Therapeutics, Inc.

SECOND: The foregoing amendment was adopted by the Corporation's Board of Directors and Stockholders on August 5, 2005.

THIRD: This Certificate of Amendment is filed by authority of the duly elected Board of Directors and Stockholders in accordance with Sections 228 and 242 of the General Corporation Law of the State of Delaware.

IN WITNESS WHEREOF, this Certificate of Amendment has been executed by the Corporation's authorized officer this 5th day of August, 2005.

BIOMIMETIC PHARMACEUTICALS, INC.

By: /s/Samuel E Lynch
Samuel E. Lynch
President and Chief Executive Officer

State of Delaware
Secretary of State
Division of Corporations
Delivered 08:02 PM 08/05/2005
FILED 07:53 PM 08/05/2005
SRV 050649698 - 3394448 FILE

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